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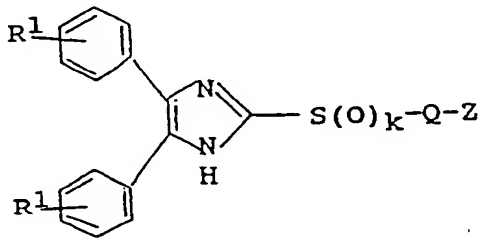

(II)

(57) Abstract

Imidazole derivates of general formula (II) in which R^1 is hydrogen or one or more substituents, k is 0, 1 or 2, Q is a straight or branched alkylene group and Z is hydrogen or a substituent group and pharmaceutically acceptable salts thereof possess useful pharmacological properties as inhibitors of acyl coenzyme-A: cholesterol-o-acyl transferase and as inhibitors of the binding of thromboxane TXA_2 to its receptors, and are useful in therapy.

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IMIDAZOLES

The present invention relates to new therapeutically useful imidazole derivatives, to a process for their preparation, to pharmaceutical compositions containing them, and to their use as pharmaceuticals.

The imidazole derivatives of the present invention are the compounds of the general formula:-

$$A\text{-}S(O)_k\text{-}Q\text{-}Z \qquad I$$

wherein A represents a group of general formula II shown hereinafter in the present specification, wherein the symbols R^1 may be the same or different and each represents hydrogen or one or more substituents, for example substituents selected from halogen atoms, and straight- or branched-chain alkyl and alkoxy groups containing from 1 to about 6 carbon atoms, and trifluoromethyl groups;

k represents 0, 1 or 2;

Q represents a methylene group or alkylene chain containing from 2 to about 5 carbon atoms, optionally substituted with one or more alkyl groups containing from 1 to about 4 carbon atoms; and

Z represents a hydrogen atom; a hydroxy group; an alkoxy group optionally substituted by, for example, an alkoxy or alkoxyalkoxy group; an aryl, for example phenyl, group optionally substituted by, for example,

one or more alkoxy, e.g. methoxy, groups; a dialkylamino group wherein the alkyl groups may be the same or different and each is straight- or branched-chain and contains from 1 to about 4 carbon atoms; a group of the formula $-NHR^2$, wherein R^2 represents an acyl group, for example a straight- or branched-chain alkanoyl group containing up to about 6 carbon atoms and which may be substituted, for example, by a carboxy group, or R^2 represents a group of the formula $-C(SR^3)=N-CN$ wherein R^3 represents a straight- or branched-chain alkyl group containing from 1 to about 3 carbon atoms, or R^2 represents a 5- or 6-membered nitrogen-containing heterocyclic ring optionally substituted by one or more substituents selected from, for example, amino groups and straight- or branched-chain alkyl groups containing from 1 to about 3 carbon atoms, and preferably attached to the group -NH via a carbon atom; or Z represents a group of the formula $-COR^4$ wherein R^4 represents a straight- or branched-chain alkyl group containing from 1 to about 3 carbon atoms; a group of the formula $-CH(OH)R^5$, $-COR^5$, $-CSR^5$, $-CONHR^5$ or $-CSNHR^5$ wherein R^5 represents a 5- or 6-membered nitrogen-containing heterocyclic ring which may also contain an oxygen atom, optionally substituted by one or more substituents selected from, for example, straight- or branched-chain alkyl groups containing from 1 to about 3 carbon atoms; an alkynyl or cycloalkyl group

containing up to about 6 carbon atoms; a group of the formula $-CH(R^6)OR^7$ wherein R^6 represents a straight- or branched-chain alkenyl or alkoxy group containing up to about 6 carbon atoms and R^7 represents a straight- or branched-chain alkyl group containing from 1 to about 4 carbon atoms, optionally substituted by one or more substituents selected from, for example, hydroxy groups; a group of the general formula III shown hereinafter, wherein m is 0 or 1, n is 0 or 1 and p is 1, 2 or 3, and the symbols R^8 each represent a hydrogen atom, or a methyl group substituted by a straight- or branched-chain alkoxyy or alkanoyloxy group containing up to about 6 carbon atoms; a group of the general formula IV shown hereinafter wherein m is as hereinbefore defined; a group of the general formula V shown hereinafter wherein R^9 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to about 4 carbon atoms and R^{10} represents a hydrogen atom or a hydroxy group or a straight- or branched-chain alkyl group containing from 1 to about 4 carbon atoms; or a group of the general formula VI shown hereinafter wherein R^9 is as hereinbefore defined; a group of the general formula VII shown hereinafter wherein R^9 and R^{10} are as hereinbefore defined, the symbols R^{11} may be the same or different and each represents a hydrogen atom or a

hydroxy group and R^{12} represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to about 4 carbon atoms; or a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{13}$ wherein R^9 and R^{10} are as hereinbefore defined, r represents 0 or 1 and R^{13} represents a hydroxy group or a straight- or branched-chain alkoxy or alkylamino group containing from 1 to about 4 carbon atoms; and pharmaceutically acceptable salts thereof.

In this specification alkyl groups and moieties, unless otherwise specified, are straight- or branched-chain and contain from 1 to about 6 carbon atoms.

(2S,4R,6S)-6-[(4,5-Diphenylimidazol-2-yl)-thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran and (2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)-thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran are excluded from the scope of this invention.

Especially important features of the present invention are, or involve, compounds of general formula I wherein at least one of the symbols has a value selected from the following:-

(i) the symbols R^1 may be different or, preferably, the same and each represents a hydrogen or halogen, e.g. chlorine or fluorine, atom or a straight- or branched-chain alkyl group containing from 1 to 6, preferably from 1

to 4, carbon atoms, or a straight- or branched-chain alkoxy group containing from 1 to 3 carbon atoms, e.g. methoxy, or a trifluoromethyl group;

(ii) k represents 0;

(iii) Z represents a hydrogen atom; a hydroxy group; an alkoxy, e.g. ethoxy, group optionally substituted by, for example, an alkoxyalkoxy, e.g. methoxyethoxy, group; an aryl, for example phenyl, group optionally substituted by, for example, one or more alkoxy, e.g. methoxy, groups; a dialkylamino group wherein the alkyl groups may be the same or different and each is straight- or branched-chain and contains from 1 to 4, preferably from 1 to 3, carbon atoms; an ethynyl group, or a cycloalkyl, e.g. cyclohexyl, group;

(iv) R^2 represents an acyl group, for example a straight- or branched chain alkanoyl group containing up to about 6 carbon atoms and which may be substituted, for example, by a carboxy group; or a pyridyl or triazolyl group optionally substituted by one or more, preferably one or two, substituents selected from amino groups and straight- or branched-chain alkyl, e.g. methyl, groups;

(v) R^3 represents a methyl group;

(vi) R^4 represents a methyl group;

(vii) R^5 represents a imidazolyl, morpholinyl or pyridyl group optionally substituted by one or two alkyl, e.g. methyl, groups;

(viii) R^6 represents an allyl group, or an alkoxy group containing from 1 to 3 carbon atoms, e.g. methoxy or ethoxy;

(ix) R^7 represents an alkyl group containing from 1 to 3 carbon atoms, e.g. methyl or ethyl, optionally substituted by a hydroxy group;

(x) R^8 represents a hydrogen atom or a hydroxymethyl, methoxymethyl or acetoxymethyl group;

(xi) R^9 represents a hydrogen atom or a methyl group;

(xii) R^{10} represents a hydrogen atom or a hydroxy or methyl group;

(xiii) R^{12} represents a hydrogen atom or a methyl group; and/or

(xiv) R^{13} represents an alkoxy or alkylamino group containing from 1 to 4 carbon atoms;

the other symbols being as hereinbefore defined, and pharmaceutically acceptable salts thereof.

Particularly important features of the present invention are, or involve, at least one of the following compounds:-

A 2-(2-ethoxyethylthio)-4,5-diphenylimidazole

B 2-[(dioxolan-2-yl)methylthio]-4,5-diphenyl-imidazole

C 2-benzylthio-4,5-diphenylimidazole

D 2-(3,5-dimethoxybenzylthio)-4,5-diphenyl-imidazole

E 2-cyclohexylmethylthio-4,5-diphenylimidazole

F [±]-2-[(tetrahydro-2H-pyran-6-yl)methylthio]-4,5-diphenylimidazole

G [±]-2-[(tetrahydro-2H-pyran-6-yl)methylthio]-4(5)-(4-chlorophenyl)-5(4)-phenylimidazole

H 2-[2-(1,3-dioxan-2-yl)ethylthio]-4,5-diphenyl-imidazole

I 2-[3-(1,3-dioxan-2-yl)propylthio]-4,5-diphenyl-imidazole

J 2-(2,2-diethoxyethylthio)-4,5-diphenylimidazole

K 2-(2,2-dimethoxyethylthio)-4,5-diphenyl-imidazole

L 2-(3,3-diethoxypropylthio)-4,5-diphenyl-imidazole

M 2-(4-ethoxyhex-5-enylthio)-4,5-diphenyl-imidazole

N 2-[4-(2-hydroxyethyl)hept-6-enylthio]-4,5-

diphenylimidazole

O 2-(2-oxoprop-1-yl)thio-4,5-diphenylimidazole

P 2-(2-diethylaminoethylthio)-4,5-diphenyl-imidazole

Q 2-(2-diisopropylaminoethylthio)-4,5-diphenyl-imidazole

R 2-propargylthio-4,5-diphenylimidazole

S [±]-4,5-bis(2-chlorophenyl)-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole

T [±]-4(5)-(2-chlorophenyl)-5(4)-phenyl-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole

U [±]-4(5)-(3-chlorophenyl)-5(4)-phenyl-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole

V [±]-2-[(1,4-dioxanyl)methylthio]-4,5-diphenyl-imidazole

W [±]-2-[(2,2-di(methoxymethyl)tetrahydro-2H-pyran-6-yl)methylthio]-4,5-diphenylimidazole

X 2-(3-dimethylaminopropylthio)-4,5-diphenyl-imidazole

Y 2-(3,6,9-trioxadecylthio)-4,5-diphenylimidazole

Z [±]-2-[2,2-di(hydroxymethyl)tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenylimidazole

AA [±]-2-[2,2-di(acetoxymethyl)tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenylimidazole

AB 2-(2-hydroxyethylthio)-4,5-diphenylimidazole

AC 2-ethylthio-4,5-diphenylimidazole

AD 2-[(1,3-dioxan-2-yl)methylthio]-4,5-diphenyl-imidazole

AE 3-cyano-2-methyl-1-[3-(4,5-diphenylimidazol-2-ylthio)propyl]isothiourea

AF 2-[2-(5-amino-1,2,4-triazol-3-ylamino)ethyl-thio]-4,5-diphenylimidazole dihydrochloride

AG 3-cyano-2-methyl-1-[4-(4,5-diphenylimidazol-2-ylthio)butyl]isothiourea

AH 2-[4-(5-amino-1,2,4-triazol-3-ylamino)butyl-thio]-4,5-diphenylimidazole

AI 2-[3-(5-amino-1,2,4-triazol-3-ylamino)propyl-thio]-4,5-diphenylimidazole

AJ 3-cyano-2-methyl-1-[2-(4,5-diphenylimidazol-2-ylthio)ethyl]isothiourea

AK N-(4-methylpyrid-2-yl)-4-(4,5-diphenyl-imidazol-2-ylthio)butanamide

AL 4,6-dimethyl-2-[4-(4,5-diphenylimidazol-2-yl-thio)butylamino]pyridine

AM 2-(3-acetamidopropylthio)-4,5-diphenylimidazole

AN 2,6-dimethyl-N-[4-(4,5-diphenylimidazol-2-yl-thio)butan-1-oyl]morpholine

AO N-(4,6-dimethylpyrid-2-yl)-4-(4,5-diphenyl-imidazol-2-ylthio)butanamide

AP N-(pyrid-2-yl)-4-(4,5-diphenylimidazol-2-ylthio)butanamide

AQ (5R,5S)-4,5-diphenyl-2-[(2-oxotetrahydrofur-5-

yl)methylthio]imidazole

AR (4R,4S)(6R,6S)-6-[(4,5-bis{3-chlorophenyl}imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

AS (4R,4S)(6R,6S)-6-[(4,5-Bis{4-chlorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

AT (4R,4S)(6R,6S)-6-[(4,5-Bis{2-chlorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

AU (4R,4S)(6R,6S)-6-[(4,5-Bis{4-fluorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

AV (4R,4S)(6R,6S)-6-[(4,5-Bis{4-trifluoromethylphenyl}imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

AW (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{3-methylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

AX (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{4-methylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

AY (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{4-isopropylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

AZ (4R,4S)(6R,6S)-6-[(4,5-Bis{4-tertbutylphenyl}-

imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyl-tetrahydropyran-2-one

BA (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{2-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

BB (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{3-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

BC 6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

BD 6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one

BE 4-hydroxy-6-[(4,5-bis{4-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

BF 4-hydroxy-6-[(4,5-bis{4-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one

BG (6R,6S)-6-[(4,5-bis{4-methylphenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BH (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BI (6R,6S)-6-[(4,5-Bis{4-chlorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BJ (6R,6S)-6-[(4,5-bis{3-chlorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BK (6R,6S)-6-[(4,5-bis-{2-chlorophenyl}imidazol-

2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BL (6R,6S)-6-[(4,5-bis-{4-fluorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one

BM (5R,5S)-5-[(4,5-bis-{4-methylphenyl}imidazol-2-yl)thiomethyl]tetrahydrofuran-2-one

BN (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-3,4,5,6-tetrahydropyran-2-one

BO (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4,4-dimethyl-3,4,5,6-tetrahydropyran-2-one

BP (4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-3,4,5,6-tetrahydropyran-2-one

BQ (3R,3S)(5R,5S)-ethyl 6-[(4,5-diphenylimidazol-2-yl)thio]-3,5-dihydroxyhexanoate

BR (6R,6S)-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-oxo-1,4-dioxane

BS t-butyl 6-[(4,5-bis-{4-chlorophenyl}imidazol-2-yl)thio]-3,5-dihydroxy-3-methylhexanoate

BT (3R,3S)(5R,5S)-ethyl 6-[(4,5-diphenylimidazol-2-yl)thio]-3,5-dihydroxy-3-methylhexanoate

BU (2R,2S)-2-[(2-hydroxy-4,4-dimethyl-5-methylaminocarbonylpent-1-yl)thio]-4,5-diphenylimidazole

BV (2R,2S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)-thiomethyl]-2-hydroxy-3,4,5,6-tetrahydropyran

BW (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2,4-dihydroxy-4-methyltetrahydropyran

BX (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-4-methyltetrahydropyran (2-alpha-anomer)

BY (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-4-methyltetrahydropyran (2-beta-anomer)

BZ (2S,3R,4R,5S,6S)-2-[(4,5-diphenylimidazol-2-yl)thiomethyl]-6-methoxy-3,4,5-trihydroxytetrahydropyran

CA 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methylimidazole

CB 2-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-1-methylimidazole

CC 2-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]-1-methylimidazole

CD 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-imidazole

CE 2-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]-imidazole

CF 2-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-imidazole

CG 2-[4-(4,5-diphenylimidazol-2-ylthio)-1-hydroxybutyl]-1-methylimidazole

CH 2-[6-(4,5-diphenylimidazol-2-ylthio)-1-hydroxy-hexyl]-1-methylimidazole

CI 2-[5-(4,5-diphenylimidazol-2-ylthio)-1-hydroxy-pentyl]-1-methylimidazole

CJ 2-[4-(4,5-diphenylimidazol-2-ylthio)-1-hydroxy-butyl]imidazole

CK 2-[5-(4,5-diphenylimidazol-2-ylthio)-1-hydroxy-pentyl]imidazole

CL 2-[6-(4,5-diphenylimidazol-2-ylthio)-1-hydroxy-hexyl]imidazole

CM 4-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-morpholine

CN 4-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-morpholine and

CO 4-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]-morpholine.

The letters A to CO are allocated to the compounds for easy reference.

As will be apparent to those skilled in the art, many of the compounds of formula I may exist in more than one enantiomeric form. All such compounds, and their mixtures, are within formula I and within the scope of the present invention.

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT; EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts.

They are also inhibitors of the binding of thromboxane TxA_2 to its receptors. They are therefore of utility in the treatment of conditions such as thrombosis and myocardial infarction, vasospastic disorders, for example associated with angina, and bronchospasm, for example associated with asthma, or in reperfusion salvage therapy, for example after ischaemic injury.

Compounds within the scope of the present invention exhibit positive pharmacological activities as demonstrated by the following in-vitro and in-vivo tests which are believed to correlate to pharmacological activity in humans and other animals.

In in-vitro tests on human platelet membrane, compounds of the invention produced up to 50% inhibition of the binding of thromboxane TxA_2 to its receptors at concentrations down to about 600 nanomolar or less.

In assays performed in-vitro, microsomes, obtained from the livers of rats fed on a diet supplemented with 0.5%w/w cholesterol and 0.25%w/w cholic acid for 7 days, were incubated with radiolabelled oleoyl-CoA in the presence of compounds according to the invention at a concentration of 0.5 or 1 µg/ml. The degree of ACAT inhibition produced was up to 90% or more.

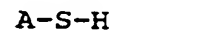
In in-vivo tests, using rats fed on a similar diet to that above and further supplemented by 0.03% w/w of test compound, the compounds according to the invention inhibited increases in plasma cholesterol concentrations, measured after 3 days, relative to control animals fed on the cholesterol supplemented diet without the drug, by up to 90% or more.

Compounds of formula I can be prepared by the application or adaptation of known methods, for example methods illustrated in the following Examples and Reference Examples.

The intermediates and starting materials from which they are prepared can also be prepared by the application or adaptation of known methods.

By the term "known methods" is meant methods known heretofore or described in the literature.

For example, as a feature of the present invention, compounds of formula I, wherein k is 0 and the other symbols are as hereinbefore defined, are prepared by the reaction of a compound of the general formula:-

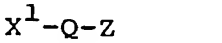


VIII

wherein A is as hereinbefore defined, or a salt thereof, of the general formula:-

IX

wherein A is as hereinbefore defined and M represents an alkali metal, with a compound of the general formula:-



X

or a salt thereof, wherein X^1 is a group displaceable by a thiolate salt, such as a halogen e.g. a chlorine, bromine or iodine, atom or an alkyl- or aryl-

sulphonyloxy group (e.g. methanesulphonyloxy or 4-toluenesulphonyloxy) and Q and Z are as hereinbefore defined. The reaction is generally carried out in an inert organic solvent such as tetrahydrofuran, dimethylformamide, a lower alkanol such as methanol or ethanol, at a temperature from ambient to 110°C and optionally in the presence of a proton acceptor, such as an amine (e.g. triethylamine or pyridine) or an alkali metal hydroxide, carbonate or alkoxide. The salt of formula IX or the compound of formula X can optionally be prepared in situ by the application or adaptation of known methods.

According to a further feature of the invention, compounds of formula I wherein k is 0 and Z represents a group of the formula $-NH-C(SR^3)=N-CN$, A, Q and R^3 being as hereinbefore defined, are prepared by the reaction of compounds of the general formula:-

$$(R^3S)-C(SR^3)=N-CN \qquad XI$$

wherein R^3 is as hereinbefore defined with compounds of the general formula:-

$$A-S-Q-NH_2 \qquad XII$$

wherein A and Q are as hereinbefore defined.

According to a further feature of the invention, compounds of formula I wherein k is 0 and Z represents a group of the formula $-NHR^2$ wherein R^2 represents an acyl group, A and Q being as hereinbefore defined, are

prepared by the acylation by known methods of compounds of formula XII as hereinbefore defined, for example by reaction with the appropriate acid anhydride or acid halide.

According to a further feature of the invention, compounds of formula I wherein k is 0 and Z represents a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{14}$ wherein R^9, R^{10} and r are as hereinbefore defined and R^{14} represents a straight- or branched-chain alkoxy group containing from 1 to 4 carbon atoms, A and Q being as hereinbefore defined, are prepared by the reaction of a compound of formula IX as hereinbefore defined, optionally prepared in situ, with a compound of the general formula:-

$$R^{15}CH_2(CR^9R^{10})_rCH_2COR^{14} \qquad XIII$$

wherein R^9, R^{10}, r and R^{14} are as hereinbefore defined and R^{15} represents a 1,2-epoxyethyl group, in an inert solvent such as methanol.

According to a further feature of the present invention, compounds of general formula I are prepared by the interconversion of other compounds of general formula I.

For example, compounds of formula I wherein k is 0 and Z represents a group of formula IV wherein m is 0 or Z represents a group of formula V wherein R^9 and R^{10} are as hereinbefore defined, A and Q being as

hereinbefore defined, are prepared by the cyclisation of compounds of formula I wherein k is 0 and Z represents a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{14}$, A, Q, R^9, R^{10}, r and R^{14} being as hereinbefore defined. The cyclisation can be carried out by reaction with a base, e.g. sodium methoxide in methanol, followed by reaction with trifluoroacetic acid.

Conversely, compounds of formula I wherein k is 0 and Z represents a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{14}$, A, Q, R^9, R^{10}, r and R^{14} being as hereinbefore defined, are prepared by the hydrolysis and esterification of compounds of formula I wherein k is 0 and Z represents a group of formula IV wherein m is 0 or Z represents a group of formula V wherein R^9 and R^{10} are as hereinbefore defined, A and Q being as hereinbefore defined, for example by reaction with a base, e.g. an aqueous solution of an alkali metal hydroxide, e.g. sodium hydroxide, followed by reaction of the resulting salt with the appropriate alkyl halide.

As another example, compounds of general formula I wherein k is 0, Z represents a group of formula III wherein n is 0, m is 1, and the symbols R^8 preferably represent hydrogen atoms, A, Q and p being as

hereinbefore defined, are prepared by the reaction of a compound of the general formula:-

$$A\text{-}S\text{-}Q\text{-}CH(R^{14})_2 \qquad XV$$

wherein A, Q and R^{14} are as hereinbefore defined with a compound of the general formula:-

$$HO\text{-}(CH_2)_p\text{-}C(R^8)_2\text{-}OH \qquad XVI$$

wherein p and R^8 are as hereinbefore defined, preferably in the presence of a catalyst such as pyridinium 4-toluenesulphonate, preferably at reflux and preferably in a solvent such as toluene.

As yet another example, compounds of general formula I wherein k is 0, Z represents a 5-amino-1,2,4-triazol-3-ylamino group, A and Q being as hereinbefore defined, are prepared by the reaction of compounds of formula I wherein k is 0 and Z represents a group of the formula $-NH-C(SR^3)=N-CN$, A, Q and R^3 being as hereinbefore defined, with hydrazine, preferably in a solvent such as ethanol or ethoxyethanol, and preferably under reflux.

As yet another example, some compounds of general formula I are prepared by the reduction of other compounds of general formula I.

For example, (i) compounds of general formula I wherein k is 0, Q represents a group of formula $-Q'CH_2-$, wherein Q' represents a methylene group or alkylene chain containing from 2 to 4 carbon atoms,

optionally substituted with one or more alkyl groups containing from 1 to about 4 carbon atoms, and Z represents a group of formula $-NHR^2$, A and R^2 being as hereinbefore defined, are prepared by the reduction of compounds of general formula I wherein k is 0, Q represents a group of formula -Q'-, and Z represents a group of formula $-CONHR^5$, A, Q' and R^5 being as hereinbefore defined, R^2 and R^5 being identical, for example by reaction with a metal hydride such as lithium aluminium hydride, in an ether such as tetrahydrofuran.

(ii) compounds of general formula I wherein k is 0 and Z represents a group of formula VII wherein R^{11} and R^{12} represent hydrogen atoms, A, R^9 and R^{10} being as hereinbefore defined, are prepared by the reduction of compounds of general formula I wherein k is 0 and Z represents a group of formula V, A, R^9 and R^{10} being as hereinbefore defined, for example by reaction with a metal hydride such as di-isobutylaluminium hydride, in an ether such as tetrahydrofuran.

(iii) compounds of general formula I wherein k is 0 and Z represents a group of formula $-CH(OH)R^5$, A, Q and R^5 being as hereinbefore defined, are prepared by the reduction of compounds of general formula I wherein k is 0 and Z represents a group of formula $-COR^5$, A, Q and R^5 being as hereinbefore defined, for example by

reaction with a metal borohydride such as sodium borohydride in a solvent system such as aqueous ethanol.

As yet another example, some compounds of general formula I are prepared by the elimination of the elements of water from other compounds of general formula I.

For example, compounds of general formula I wherein k is 0 and Z represents a group of formula VI, A, Q and R^9 being as hereinbefore defined, are prepared by the elimination of the elements of water from compounds of general formula I wherein k is 0 and Z represents a group of formula V wherein R^{10} represents a hydroxy group, A, Q and R^9 being as hereinbefore defined, e.g. by reaction with trifluoroacetic acid.

As a further example, compounds of formula I wherein k is 0 and Z represents a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{16}$, wherein R^{16} represents a straight- or branched -chain alkylamino group containing from 1 to 4 carbon atoms, A, Q, R^9, R^{10} and r being as hereinbefore defined, are prepared from compounds of formula I wherein k is 0 and Z represents a group of formula V wherein R^9 and R^{10} are as hereinbefore defined, A and Q being as hereinbefore defined, for example by reaction with the appropriate alkylamine of formula $R^{16}NH_2$, R^{16} being as hereinbefore defined,

preferably at an elevated temperature, e.g. at reflux, in a solvent such as ethanol.

As a still further example, compounds of formula I containing one or more lower alkoxy groups are prepared by the alkylation of compounds of formula I containing one or more hydroxy groups, for example by reaction with the appropriate lower alkanol, preferably in the presence of a catalyst such as boron trifluoride diethyl etherate.

As a further example, compounds of formula I wherein k is 0 and Z represents a group of the formula $-COR^5$, wherein R^5 is as hereinbefore defined, preferably an optionally substituted imidazole group, A and Q being as hereinbefore defined, are prepared by reaction of corresponding compounds of formula I wherein Z represents a morpholinocarbonyl group with the product of the reaction between lithium diisopropylamide (preferably complexed with mono-tetrahydrofuran) with a compound of formula $R^{5'}H$ wherein $R^{5'}$ represents a group within the definition of R^5 but wherein any free imino groups are temporarily protected, e.g. by dimethylaminomethyl groups.

As yet a further example, compounds of formula I wherein k represents 1 or 2, A, Q and Z being as hereinbefore defined, are prepared by the oxidation of compounds of formula I wherein A, Q and Z are as hereinbefore defined and p is less than in the desired

product.

The oxidation may be performed by using a conventional oxidant, such as hydrogen peroxide, sodium metaperiodate, a hypochlorite, an acyl nitrite, sodium perborate, peracids, such as percarboxylic acids (e.g. m-chloroperbenzoic acid), potassium permanganate or potassium hydrogen persulphate, or a ruthenium (VIII) compound, in an inert solvent, at or below room temperature.

Suitable solvents may include water, alcohols, water-alcohol mixtures, chlorinated hydrocarbons, such as dichloromethane, and organic acids.

As another example, compounds of formula I containing one or more carboxy groups are prepared by the hydrolysis by known methods of compounds of formula I containing one or more alkoxycarbonyl groups.

Compounds of general formula I wherein k is 1, the other symbols being as hereinbefore defined, may be obtained in a chirally pure form by separation of the enantiomers arising from a non-selective oxidation or by using known enantio-selective oxidising systems.

It is to be understood that, where in this specification reference is made to compounds of formula I, it is intended to refer also where the context so permits to their pharmaceutically acceptable salts. Such salts are prepared from the parent compounds of

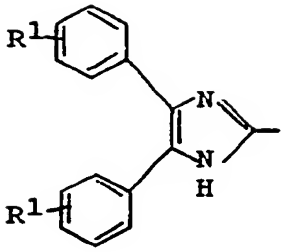
formula I by the application or adaptation of known methods, or are produced by the processes described hereinafter. Parent compounds of formula I can be generated therefrom by the application or adaptation of known methods.

Preferred salts are acid addition salts such as the hydrochlorides or, where the compound of formula I contains an acidic hydrogen atom, for example when Z contains a carboxy group, salts formed with alkali metals, e.g. sodium and potassium, or alkaline earth metals, e.g. calcium and magnesium, or with ammonia or with pharmaceutically acceptable amines.

Compounds of formula I can be purified by the usual physical means, for example by crystallisation or chromatography.

The following Examples illustrate the preparation of compounds according to the invention and the Reference Examples illustrate the preparation of intermediates.

In the presentation of the nuclear magnetic resonance ("NMR") spectra chemical shifts were expressed in parts per million relative to tetramethylsilane. Abbreviations have the following significances:- s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, and br = broad signal.



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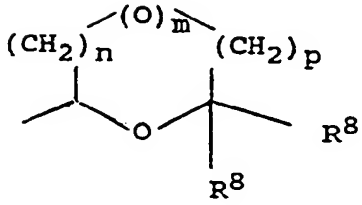

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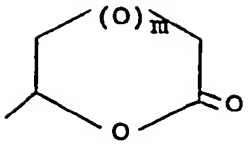

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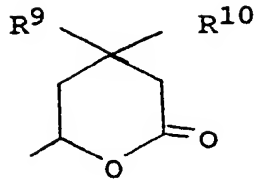

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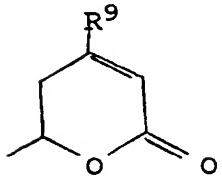

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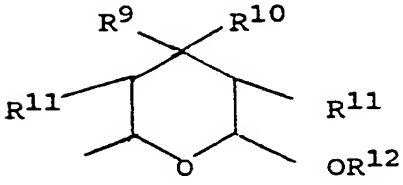


(VII)

EXAMPLE 1

Compounds A, B, C, D, E, F, G,

H, I, J, K, L, M, N, O, P, and Q

A A stirred suspension of 4,5-diphenylimidazole-2-thiol (3.2g) and anhydrous potassium carbonate (1.8g) in anhydrous dimethylformamide (50ml) was stirred at room temperature for 15 minutes. It was then treated with 2-bromoethyl ethyl ether (2.4g) and the mixture was stirred at room temperature overnight. The mixture was filtered through silica gel and the bright yellow filtrate was evaporated to low bulk. The residue was shaken with ethyl acetate (100ml) and water (50ml). The layers were separated and the organic layer was washed with water (50ml), dried (magnesium sulphate) and evaporated.

The residue was subjected to flash chromatography eluting with a mixture of ethyl acetate and dichloromethane (1:3 v/v). Crystallisation from cyclohexane gave 2-(2-ethoxyethylthio)-4,5-diphenyl-imidazole (2.2g) in the form of a white crystalline solid, m.p. 91-92°C.

[Elemental analysis:- C,69.9;H,6.1;N,8.5;S,10.0%;
Calculated:- C,70.34;H,6.21;N,8.64;S,9.88%.
NMR (in CDCl3):- 1.23 (3H,t,J = 8Hz), 3.18 (2H,t,J = 6Hz), 3.64 (2H,q,J = 8Hz), 3.83 (2H,t,J = 6Hz), 7.2-7.6 (10H,m)].

By proceeding in a similar manner, but replacing the 2-bromoethyl ethyl ether used as a starting material by the appropriate quantity of the corresponding halides, and optionally replacing the potassium carbonate by potassium t-butoxide, there were prepared the following compounds:-

B 2-[(dioxolan-2-yl)methylthio]-4,5-diphenyl-imidazole, m.p. 139-140°C.;

C 2-benzylthio-4,5-diphenylimidazole, m.p. 181-189°C.;

D 2-(3,5-dimethoxybenzylthio)-4,5-diphenylimidazole, m.p. 148.5-149.5°C.;

E 2-cyclohexylmethylthio-4,5-diphenylimidazole, m.p. 169-171°C.;

F [±]-2-[(tetrahydro-2H-pyran-6-yl)methylthio]-4,5-diphenylimidazole, m.p. 143-145°C.;

G [±]-2-[(tetrahydro-2H-pyran-6-yl)methylthio]-4(5)-(4-chlorophenyl)-5(4)-phenylimidazole, m.p. 127-129°C.;

H 2-[2-(1,3-dioxan-2-yl)ethylthio]-4,5-diphenyl-imidazole, m.p. 191-193°C.;

I 2-[3-(1,3-dioxan-2-yl)propylthio]-4,5-diphenyl-imidazole, m.p. 151°C.;

J 2-(2,2-diethoxyethylthio)-4,5-diphenylimidazole, m.p. 90-94°C.;

K 2-(2,2-dimethoxyethylthio)-4,5-diphenyl-

imidazole, m.p. 162-163°C.;

L 2-(3,3-diethoxypropylthio)-4,5-diphenyl-imidazole, m.p. 247-249°C.;

M 2-(4-ethoxyhex-5-enylthio)-4,5-diphenyl-imidazole, m.p. 91°C.;

N 2-[4-(2-hydroxyethyl)hept-6-enylthio]-4,5-diphenylimidazole, in the form of a colourless gum;

O 2-(2-oxoprop-1-yl)thio-4,5-diphenylimidazole, m.p. 145-147°C; and

P 2-(2-diethylaminoethylthio)-4,5-diphenyl-imidazole, m.p. 90-92°C;

Q By again proceeding in a similar manner, but replacing the 2-bromoethyl ethyl ether by 2-diisopropylaminoethyl chloride hydrochloride and the potassium carbonate by potassium t-butoxide, and treating a solution of the free base in ethanol with a solution of hydrogen chloride in ethanol [prepared by adding acetyl chloride (12ml) dropwise to cold ethanol (100ml;10°C) with stirring, maintaining the temperature below 30°C] there was prepared 2-(2-diisopropylamino-ethylthio)-4,5-diphenylimidazole, m.p.183-185°C. [Elemental analysis:- C,60.8;H,7.1;N,9.;S,7.3;Cl,14.4%; Calculated ($C_{23}H_{29}N_3S$:1.8HCl:0.5H_2O):- C,60.8;H,7.05; N,9.25;S,7.06;Cl,14.05%].

EXAMPLE 2

Compound R

A stirred suspension of lithium hydroxide hydrate (4.2g) in ethanol (200ml) was treated, portionwise, with 4,5-diphenylimidazole-2-thiol. The mixture was stirred at ambient temperature for 30 minutes and then it was treated with propargyl chloride (7.45g), and stirring was continued for a further 3 hours. The reaction mixture was poured into water with stirring, and the resulting solid was filtered off, washed with water and dried. Recrystallisation from a mixture of petroleum ether (b.p.40-60°C) and dichloromethane, and then from toluene, gave 2-propargylthio-4,5-diphenylimidazole (16.07g) in the form of a white solid, m.p. 164-166°C. [Elemental analysis:- C,74.2;H,4.73;N,9.6;S,10.9%; Calculated:- C,74.45;H,4.86;N,9.65;S,11.04%].

EXAMPLE 3

Compounds S, T and U

S A stirred suspension of 4,5-bis(2-chlorophenyl)-imidazole-2-thiol (2.0g) in anhydrous methanol (20ml) was treated with sodium methoxide (0.41g) and then stirred at room temperature for 5 minutes. The mixture was then treated with 2-bromomethyltetrahydro-2H-pyran (2.0g) and stirred at reflux for 2 hours. After cooling to room temperature the mixture was

poured into water (250ml) and the precipitate was filtered off. The product was dissolved in dichloromethane (100ml) and the solution was dried (magnesium sulphate) and evaporated. Trituration of the residue with diethyl ether gave a white solid, which was crystallised from methanol, to give [±]-4,5-bis(2-chlorophenyl)-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole (1.85g) in the form of a white powder, m.p. 162-4°C.

[Elemental analysis:- C,60.2;H,4.82;N,6.82;S,7.5%;

Calculated:- C,60.15;H,4.81;N,6.68;S,7.65.

NMR (in $CDCl_3$):- 1.5-2.0 (6H,m), 3.03 (1H,dd,J = 8Hz, 6Hz), 3.27 (1H,dd,J = 12Hz, 2Hz), 3.59 (1H,dt,J = 12Hz, 2Hz), 3.72 (1H,m), 4.21 (1H,dt,J = 10Hz, 2Hz)].

By proceeding in a similar manner, but replacing the 4,5-bis(2-chlorophenyl)imidazole-2-thiol with the appropriate quantity of the corresponding imidazole-2-thiol, there were prepared:-

T [±]-4(5)-(2-chlorophenyl)-5(4)-phenyl-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole, m.p. 58-60°C.; and

U [±]-4(5)-(3-chlorophenyl)-5(4)-phenyl-2-[(tetrahydro-2H-pyran-2-yl)methylthio]imidazole, m.p. 113-5°C.

EXAMPLE 4

Compounds V, W, X and Y

V A stirred suspension of 4,5-diphenylimidazole-2-thiol (4.2g) in anhydrous tetrahydrofuran (60ml) was treated with sodium hydride (80% dispersion in oil, 0.67g) under an argon atmosphere. After stirring at room temperature for 30 minutes the mixture was treated with [±]-2-iodomethyl-1,4-dioxane (4.2g). The resulting mixture was stirred at room temperature for 2 days, and then it was poured into water (500ml) and the product was filtered off and dried at 60°C.

Crystallisation from a mixture of isopropanol and diethyl ether gave [±]-2-[(1,4-dioxanyl)methyl-thio]-4,5-diphenylimidazole (1.14g), m.p. 144-147°C. [Elemental analysis:- C,68.0;H,5.69;N,8.2;S,9.0%; Calculated:- C,68.18;H,5.68;N,7.95;S,9.10%. NMR (in $CDCl_3$):- 3.04 (1H,dd,J = 14Hz, 8Hz), 3.13 (1H,dd,J = 16Hz, 4Hz), 3.52 (1H,t,J = 10Hz), 3.6-4.0 (6H,m), 7.2-7.7 (10H,m).

By proceeding in a similar manner, but replacing the [±]-2-iodomethyl-1,4-dioxane by the appropriate quantity of the corresponding halide, and optionally carrying out the reaction in the presence of triethylamine at temperatures from ambient to the reflux temperature, there were prepared:-

W [±]-2-[(2,2-di(methoxymethyl)tetrahydro-2H-

pyran-6-yl)methylthio]-4,5-diphenylimidazole, m.p. 143-145°C.; and

X 2-(3-dimethylaminopropylthio)-4,5-diphenylimidazole, m.p. 138-140°C.

By again proceeding in a similar manner, but replacing the [±]-2-iodomethyl-1,4-dioxane by the appropriate quantity of 10-tosyloxy-2,5,8-trioxadecane and carrying out the reaction at 40-50°C for 150 minutes, there was prepared:-

Y 2-(3,6,9-trioxadecylthio)-4,5-diphenylimidazole, in the form of a yellow oil.

[Elemental analysis ($C_{22}H_{26}N_2O_3S$:0.5CH_3OH):- C,64.9;H,6.59;N,6.69;S,7.8%;

Calculated:- C,65.2;H,6.58;N,6.76;S,7.7%].

EXAMPLE 5

Compounds Z and AA

Z A stirred suspension of 4,5-diphenylimidazole-2-thiol (2.9g) in anhydrous tetrahydrofuran (40ml) was treated with sodium hydride (80% dispersion in oil, 0.36g)under an argon atmosphere. The mixture was stirred at room temperature for 30 minutes and then it was treated with [±]-2,2-di(acetoxymethyl)-6-iodomethyltetrahydro-2H-pyran (4.9g). The resulting mixture was stirred at room temperature for 24 hours, poured into water (500ml), and the product was extracted into diethyl ether (100ml). The ethereal

solution was washed with water (50ml), dried (magnesium sulphate), and evaporated. The brown gummy residue was subjected to flash chromatography (eluting with a mixture of methanol and dichloromethane; 1:9 v/v) to give crude [±]-2-[2,2-di(acetoxymethyl)tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenylimidazole (4.8g).

A mixture of this product and potassium hydroxide (1.68g) in ethanol (25ml) and water (5ml) was stirred at room temperature for 75 minutes. The mixture was then evaporated to low bulk, diluted with water (40ml) and extracted with ethyl acetate (100ml, then 2x50ml). The resulting organic solution was dried (magnesium sulphate) and evaporated and the residue was crystallised from a mixture of methanol and ethyl acetate, to give [±]-2-[2,2-di(hydroxymethyl)-tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenyl-imidazole (1.54g), m.p. 176-178°C.

[Elemental analysis:- C,67.1;H,6.43;N,6.7;S,7.9%, Calculated:- C, 67.32;H,6.34;N,6.83;S,7.80%.

NMR (in a mixture of $CDCl_3$ and D_2O):- 1.2-1.8 (6H,m), 2.79 (1H,dd,J = 10Hz, 12Hz), 3.07 (1H,dd,J = 12Hz, 2Hz), 3.49 (2H,m), 3.69 (1H,d,J = 10Hz), 3.81 (1H,dt,J = 10Hz, 2Hz), 4.14 (1H,d,J = 10Hz), 7.2-7.6 (10H,m)].

AA A solution of [±]-2-[2,2-di(hydroxymethyl)-tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenyl-

imidazole (1.2g) in pyridine (5ml) was treated with acetic anhydride (0.92g) and the mixture was stirred at room temperature overnight. The mixture was treated with a further quantity of acetic anhydride (0.92g) in pyridine (5ml), followed, after one hour, by methanol (20ml). Evaporation of the mixture gave a colourless gum. The residue was treated with a mixture of water (20ml) and methanol (20ml) and it was evaporated again. This procedure was repeated three times, and then the residue was dissolved in ethyl acetate (25ml). This solution was dried (magnesium sulphate) and evaporated to give a pale yellow glass. This was triturated with a mixture diethyl ether and pentane to give [±]-2-[2,2-di(acetoxymethyl)tetrahydro-2H-pyran-6-ylmethylthio]-4,5-diphenylimidazole (1.0g) in the form of a stable meringue, m.p. 50-56°C.
[Elemental analysis:- C,65.7;H,6.25;N,5.80;S,6.4%;
Calculated:- C,65.59;H,6.07;N,5.67;S,6.48%.
NMR (in $CDCl_3$):- 1.3-1.8 (6H,m), 1.82 (3H,s), 2.07 (3H,s), 2.93 (1H,dd,J = 16Hz, 8Hz), 3.05 (1H,dd,J = 10Hz, 2Hz), 3.95 (2H,m), 4.02 (1H,d,J = 12Hz), 4.11 (1H,d,J = 12Hz), 4.85 (1H,d,J = 12Hz), 7.2-7.6 (10H,m)].

EXAMPLE 6

Compounds AB and AC

AB A mixture of 4,5-diphenylimidazole-2-thiol (5.0g) and 2-bromoethanol (2.5g) in ethanol (150ml) was stirred at reflux for 4 hours. The mixture was filtered hot, cooled to 5°C., neutralised by treatment with sodium hydroxide solution (2M) and poured into iced water (1500ml). The resulting cream solid (4.8g) was filtered off and subjected to flash chromatography (eluting with a mixture of dichloromethane and methanol (19:1 v/v) followed by crystallisation from ethanol, to give 2-(2-hydroxy-ethylthio)-4,5-diphenylimidazole (0.7g), in the form of a white crystalline solid, m.p. 168-70°C. [Elemental analysis:- C,68.7;H,5.5;N,9.4;S,10.6%; Calculated:- C,68.9;H,5.45;N,9.45;S,10.81%. NMR (in CD_3SOCD_3):- 3.20 (2H,t,J = 8Hz), 3.68 (2H,t,J = 8Hz), 7.2-7.5 (10H,m)].

AC By proceeding in a similar manner, but replacing the 2-bromoethanol by bromoethane, there was prepared:- 2-ethylthio-4,5-diphenylimidazole, m.p. 190°C.

EXAMPLE 7

Compound AD

A mixture of 2-(2,2-diethoxyethylthio)-4,5-diphenylimidazole (10.0g), pyridinium 4-toluene-

sulphonate, polymer-bound (1.6g; approximately 6mmole of active component), and 1,3-propanediol (10.0g) in toluene (500ml) was stirred at reflux under a Dean and Stark water trap for 24 hours. At periodic intervals of about one hour the fluid collected in the water trap was run off and replaced in the reaction flask by fresh toluene. After cooling to room temperature, the mixture was washed with water (3x250ml), dried (magnesium sulphate) and evaporated. The resulting dark orange oil was subjected to flash chromatography (eluting with mixtures of ethyl acetate and dichloromethane; 1:9-4:6 v/v) and crystallised from ethyl acetate, to give 2-[(1,3-dioxan-2-yl)methylthio]-4,5-diphenylimidazole, (2.3g) m.p. 153-155°C.

[Elemental analysis:- C,68.3;H,5.75;N,7.9;S,9.1%;
Calculated:- C,68.15;H,5.72;N,7.95;S,9.10%.
NMR (in $CDCl_3$):- 1.38 (1H,m), 2.10 (1H,m) 3.11 (2H,d,J = 6Hz), 3.87 (2H,dt,J = 10Hz, 2Hz), 4.16 (2H,dd,J = 10Hz, 6Hz), 4.89 (1H,t,J = 6Hz), 7.2 7.5 (10H,m)].

EXAMPLE 8

Compounds AE, AG and AJ

AE A stirred solution of 2-(3-aminopropylthio)-4,5-diphenylimidazole (3.36g) in ethanol (150ml) at the ambient temperature was treated with S,S'-dimethyl-N-

cyanodithioiminocarbonate (1.76g), and stirred for one hour. The resulting solid was filtered off, washed with diethyl ether and dried, to give 3-cyano-2-methyl-1-[3-(4,5-diphenylimidazol-2-ylthio)propyl]isothiourea (3.15g) in the form of a colourless solid, m.p. 225-227°C.

[Elemental analysis:- C,61.8;H,5.3;N,17.1;S,15.6%; calculated:- C,61.92;H,5.16;N,17.20;S,15.72%.

NMR (in a mixture of CD_3SOCD_3 and D_2O):- 1.94 (2H, quin,J = 7Hz), 2.53 (3H,s), 3.13 (2H,t,J = 7Hz), 3.44 (2H,t,J = 7Hz), 7.1-7.5 (10H,m)].

AG By proceeding in a similar manner, but replacing the 2-(3-aminopropylthio)-4,5-diphenylimidazole with the appropriate quantity of 2-(4-aminobutylthio)-4,5-diphenylimidazole, stirring for a total of 5 hours and, after evaporation of the reaction mixture, subjecting the residue to mplc (using a mixture of dichloromethane and methanol; 19:1 v/v) as eluent, there was prepared 3-cyano-2-methyl-1-[4-(4,5-diphenylimidazol-2-ylthio)-butyl]isothiourea (4.4g) in the form of a colourless solid, m.p.103-105°C. (from isopropanol).

[Elemental analysis:- C,62.5;H,5.46;N,16.5;S,15.3%; Calculated:- C,62.68;H,5.50;N,16.61;S,15.21%.

NMR (in a mixture of CD_3SOCD_3 and D_2O):- 1.67 (4H,m), 2.54 (3H,s), 3.13 (2H,t,J= 7Hz), 3.3-3.36 (2H,m), 7.2-7.47 (10H,m)].

AJ By again proceeding in a similar manner, but replacing the 2-(3-aminopropylthio)-4,5-diphenyl-imidazole with 2-(2-aminoethylthio)-4,5-diphenyl-imidazole, there was prepared 3-cyano-2-methyl-1-[2-(4,5-diphenylimidazol-2-ylthio)-ethyl]isothiourea (3.02g) in the form of a colourless solid, m.p. 215-217°C. (from ethanol). [Elemental analysis:- C,61.2;H,4.96;N,18.1;S,16.2%; Calculated:- C,61.04;H,4.87;N,17.80;S,16.30%.NMR (in a mixture of CD_3SOCD_3 and D_2O):- 2.38 (3H,s), 3.35 (2H,t,J= 7Hz), 3.74 (2H,t,J = 7Hz), 7.1-7.55 (10H,m)].

EXAMPLE 9

Compound AF

AF A suspension of 3-cyano-2-methyl-1-[2-(4,5-diphenylimidazol-2-ylthio)ethyl]isothiourea (1.6g) in ethanol (100ml) was treated with hydrazine hydrate (0.6ml). The mixture was heated under reflux for 2 hours, and the resulting solution was evaporated. The residue was dissolved in ethanol (250ml) and was then treated with a solution of acetyl chloride (5ml) in ethanol (20ml) with ice cooling. After stirring for 10 minutes, the solution was evaporated and the residue was dissolved in methanol (20ml). The

solution was treated with diethyl ether (60ml) and left to stand for 20 hours. The resulting solid was filtered off and dried, to give 2-[2-(5-amino-1,2,4-triazol-3-ylamino)ethylthio]-4,5-diphenylimidazole dihydrochloride (1.03g) in the form of a colourless solid, m.p. 223-226°C.

[Elemental analysis:- C,49.2;H,4.5;Cl,15.1;N,21.3; S,7.1:H_2O,3.2%;

Calculated (for $C_{19}H_{19}N_7S$:2HCl:H_2O):- C,48.72;H,4.91;Cl,15.17;N,20.94;S,6.84%.

NMR (in D_2O):- 3.46-3.66 (4H,m), 7.36-7.54 (10H,m).

Example 10

Compounds AI and AH

AI A suspension of 3-cyano-2-methyl-1-[3-(4,5-diphenylimidazol-2-ylthio)propyl]isothiourea (2.2g) in ethoxyethanol (200ml) was treated with hydrazine hydrate (3.14ml). The mixture was heated under reflux for 6 hours, and the resulting solution was evaporated. The residue was triturated with hot acetonitrile (100ml), and the resulting solid was collected and dried, giving 2-[3-(5-amino-1,2,4-triazol-3-ylamino)propylthio]-4,5-diphenylimidazole (1.45g) in the form of a colourless solid, m.p. 225-227°C.

[Elemental analysis:- C,61.6;H,5.5;N,24.6;S,8.3%;

Calculated:- C,61.36;H,5.41;N,25.04;S,8.19%.

NMR (in a mixture of CD_3SOCD_3 and D_2O):- 1.87 (2H,quin,J= 7Hz), 3.1-3.17 (4H,m), 7.16-7.50 (10H,m)].

AH By proceeding in a similar manner, but substituting ethanol for the ethoxyethanol and 3-cyano-2-methyl-1-[4-(4,5-diphenylimidazol-2-ylthio)butyl]isothiourea for the 3-cyano-2-methyl-1-[3-(4,5-diphenylimidazol-2-ylthio)propyl]-isothiourea, there was prepared:-

2-[4-(5-amino-1,2,4-triazol-3-ylamino)butylthio]-4,5-diphenylimidazole in the form of a colourless solid, m.p. 214-216°C. (from isopropanol).

[Elemental analysis:- C,62.0;H,5.7;N,24.0;S,8.2%; Calculated:- C,62.2;H,5.72;N,24.18;S,7.91%.

NMR (in a mixture of CD_3SOCD_3 and D_2O):- 1.57-1.74 (4H,m), 3.03 (2H,t,J = 7Hz), 3.13 (2H,t,J = 7Hz), 7.17-7.48 (10H,m)].

EXAMPLE 11

Compound AM

A suspension of 2-(3-aminopropylthio)-4,5-diphenylimidazole (1.55g; prepared as described in Reference Example 1) in acetic anhydride (10ml) was heated at 100°C for 3 minutes and then it was allowed to cool to the ambient temperature. The solution was then poured into water (50ml) and the mixture was allowed to stand for 90 minutes. The solution was treated with aqueous sodium hydroxide solution (2N) until it was

alkaline, and the mixture was then extracted with dichloromethane (2x30ml). The combined extracts were dried (MgSO4) and evaporated, to give a colourless solid, which was recrystallised from acetonitrile, to give 2-(3-acetamidopropylthio)-4,5-diphenylimidazole (1.08g) in the form of a colourless solid, m.p. 180-181°C. [Elemental analysis:- C,68.7;H,6.1;N,12.1;S,8.9%; Calculated:- C,68.35;H,6.02;N,11.96;S,9.12%. NMR (in $CDCl_3$) 1.88 (2H,quin,J = 7Hz), 3.18 (2H,t,J = 7Hz), 3.44 (2H,q,J = 7Hz), 7.2-7.58 (10H,m), 7.65 (1H,br.t,J = 7Hz)].

Example 12

Compounds AO, AK, AN and AP

AO A stirred suspension of 4,5-diphenylimidazole-2-thiol (3.28g) in dry tetrahydrofuran (100ml) was treated with a dispersion of sodium hydride on oil (0.6g; 60%) at ambient temperature. After stirring at ambient temperature for 20 minutes. The solution was treated with 4-chloro-N-(4,6-dimethylpyrid-2-yl)butanamide (4.2g), followed by triethylamine (5ml). The resulting mixture was heated at reflux for 20 hours and then diluted with water (180ml) and diethyl ether (80ml). The organic layer was separated and extracted with dilute hydrochloric acid (100ml;1N). The acidic aqueous phase was then separated, made alkaline by treatment with aqueous sodium hydroxide solution (1N)

and then extracted with diethyl ether (2x150ml). The combined extracts were dried (MgSO4) and evaporated, to give a solid residue, which was recrystallised from acetonitrile, to give N-(4,6-dimethylpyrid-2-yl)-4-(4,5-diphenylimidazol-2-ylthio)butanamide (2.5g) in the form of a colourless solid, m.p. 186-188°C.

[Elemental analysis:- C,70.4;H,5.81;N,12.6;S,6.6%;

Calculated:- C,70.56;H,5.92;N,12.66;S,7.25%.

NMR (in $CDCl_3$):- 2.17 (2H,quin,J = 7Hz), 2.3 (3H,s), 2.35 (3H,s), 2.62 (2H,t,J = 7Hz), 3.1 (2H,t,J = 7Hz), 6.74 (1H,s), 7.23-7.57 (10H,m), 7.79 (1H,s), 8.22 (1H,br.s)].

AK By proceeding in a similar manner, but substituting the appropriate quantity of 4-chloro-N-(4-methylpyrid-2-yl)butanamide for the 4-chloro-N-(4,6-dimethylpyrid-2-yl)butanamide, there was prepared:-

N-(4-methylpyrid-2-yl)-4-(4,5-diphenylimidazol-2-ylthio)butanamide in the form of a colourless solid, m.p. 147-149°C.

[Elemental analysis:- C,69.5;H,5.7;N,13.0;S,7.7%;

Calculated:- C,70.09;H,5.61;N,13.08;S,7.48%.

NMR (in $CDCl_3$):- 2.19 (2H,quin,J = 7Hz), 2.35 (3H,s), 2.65 (2H,t,J = 7Hz), 3.14 (2H,t,J = 7Hz), 6.86 (1H,d,J = 6Hz), 7.2-7.63 (10H,m), 7.97 (1H,s), 8.02 (1H,d,J = 6Hz), 8.49 (1H,br.s)].

AN By proceeding in a similar manner, but substituting the appropriate quantity of N-(4-chlorobutanoyl)-2,6-dimethylmorpholine for the 4-chloro-N-(4,6-dimethylpyrid-2-yl)butanamide , there was prepared:- 2,6-dimethyl-N-[4-(4,5-diphenylimidazol-2-ylthio)-butan-1-oyl]morpholine (4.7g) in the form of a colourless solid, m.p. 147-149°C.
[Elemental analysis:- C,68.6;H,6.79;N,9.7;S,7.4%; Calculated:- C,68.93;H,6.71;N,9.65;S,7.36%.

AP By proceeding in a similar manner, but substituting the appropriate quantity of 4-chloro-N-(pyrid-2-yl)butanamide for the 4-chloro-N-(4,6-dimethylpyrid-2-yl)butanamide, there was prepared:- N-(pyrid-2-yl)-4-(4,5-diphenylimidazol-2-ylthio)butanamide (0.8g) in the form of a colourless solid, m.p. 167-169°C.
[Elemental analysis:- C,68.8;H,5.19;N,13.2%; Calculated:- C,69.54;H,5.35;N,13.52%].

Example 13

Compound AL

A stirred suspension of lithium aluminium hydride (0.42g) in dry tetrahydrofuran was treated portionwise with N-(4,6-dimethylpyrid-2-yl)-4-(4,5-diphenylimidazol-2ylthio)butanamide (2.44g) at -10°C under an argon atmosphere. The mixture was then

stirred at the ambient temperature for 2 hours. It was then treated with water (0.7ml), followed by aqueous sodium hydroxide solution (2.1ml;15%) and then water (2.1ml). After stirring for 10 minutes, the mixture was filtered and the filtrate was evaporated, to give a colourless solid. This solid was subjected to flash chromatography on silica gel, using a mixture of dichloromethane and methanol (39:1 v/v) as eluent, to give 4,6-dimethyl-2-[4-(4,5-diphenyl-imidazol-2-ylthio)butylamino]pyridine (1.64g), in the form of a colourless solid, m.p. 166-168°C. [Elemental analysis:- C,72.7;H,6.6;N,12.9;S,7.5%; Calculated:- C,72.9;H,6.54;N,13.08;S,7.48%. NMR (in $CDCl_3$):- 1.73-1.84 (4H,m), 2.18 (3H,s), 2.2 (3H,s), 3.1 (2H,t,J = 7Hz), 3.22 (2H,q,J = 7Hz), 4.63 (1H,br.t,J = 7Hz), 6.0 (1H,s), 6.27 (1H,s), 7.2-7.63 (10H,m).

EXAMPLE 14

Compounds AQ to BF

AQ Sodium methoxide (2.16g) was added to a stirred suspension of 4,5-diphenylimidazole-2-thiol (10.0g) in anhydrous methanol (250ml). After stirring at room temperature for 30 minutes methyl 4,5-epoxypentanoate (7.7g) was added and the mixture was stirred at room temperature overnight. Evaporation gave a light yellow residue, which was shaken with ethyl acetate

(250ml) and water (250ml). The layers were separated and the organic layer dried (magnesium sulphate) and evaporated. The residue was boiled with methanol (100ml) for 15 minutes and then allowed to cool to room temperature. The white insoluble solid was collected by filtration and washed with a little fresh methanol. The solution was treated with fresh methanol (100ml) and 1M sodium hydroxide solution (50ml). After standing at room temperature for 2 hours the clear solution was evaporated to dryness and shaken with ethyl acetate (200ml) and 2M acetic acid solution (150ml). The layers were separated and the organic layer dried (magnesium sulphate) and evaporated. The oily residue was dissolved in dichloromethane (300ml) and treated with trifluoroacetic acid (10ml). After standing at room temperature for 2 hours the solution was washed with 5% sodium hydrogen carbonate solution (5x150ml), dried (magnesium sulphate) and evaporated. The resulting white foam was subjected to flash chromatography (ethyl acetate-dichloromethane mixture, 1:1 v/v). Crystallisation from ethyl acetate/hexane gave (5R,5S)-4,5-diphenyl-2-[(2-oxotetrahydrofur-5-yl)methylthio]imidazole (2.0g) in the form of a dense white solid, m.p. 118-120°C.

[Elemental analysis:- C,68.7;H,5.21;N,7.9;S,9.1%;

Calculated:- C,68.55;H,5.18;N,7.99;S,9.15%.

NMR (in $CDCl_3$):- 2.10 (1H,m), 2.3-2.7 (3H,m) 3.32 (1H,m), 4.83 (1H,m), 7.2-7.5 (10H,m)].

AR By proceeding in a similar manner, but substituting 4,5-bis(3-chlorophenyl)imidazole-2-thiol for the 4,5-diphenylimidazole-2-thiol, and t-butyl 5,6-epoxy-3-hydroxy-3-methylhexanoate for the methyl 4,5-epoxypentanoate, there was prepared:- (4R,4S)(6R,6S)-6-[(4,5-bis{3-chlorophenyl}imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one in the form of a white solid, m.p. 178°C. [Elemental analysis:- C,57.1;H,4.32;Cl,15.1;N,5.88; S,6.73%; Calculated:- C,57.02;H,4.35;Cl,15.3;N,6.05; S,6.92%. NMR (in $CDCl_3$):- 1.35(3H,s), 1.66-1.8(1H,m), 2.14-2.22(1H,m), 2.4-2.78(2H,m), 3.4(2H,d,J = 4Hz), 4.41 (1H.s),4.9-5.1(1H,m)].

By again proceeding in a similar manner, and replacing the 4,5-bis(3-chlorophenyl)imidazole-2-thiol with the appropriate quantity of the corresponding imidazole-2-thiol, there were also prepared:-

AS (4R,4S)(6R,6S)-6-[(4,5-Bis{4-chlorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetra-hydropyran-2-one, m.p. 190-1°C. [Elemental analysis:- C,56.8;H,4.3;Cl,15.7;N,5.9;S,6.82%; Calculated:- C,57.02;H,4.35;Cl,15.3;N,6.05;S,6.92%].

AT (4R,4S)(6R,6S)-6-[(4,5-Bis{2-chlorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydro-

pyran-2-one, m.p. 100°C.

[Elemental analysis:- C,56.8;H,4.36;Cl,15.2;N,6.04;S,7.2%;
Calculated:- C,57.02;H,4.35;Cl,15.3;N,6.05;S,6.92%].

AU (4R,4S)(6R,6S)-6-[(4,5-Bis{4-fluorophenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one, m.p. 174-178°C.

[Elemental analysis:- C,61.7;H,4.8;F,8.9;N,6.5;S,7.4%;
Calculated:- C,61.38;H,4.68;F,8.83;N,6.51;S,7.45%].

AV (4R,4S)(6R,6S)-6-[(4,5-Bis{4-trifluoromethylphenyl}imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one, m.p. 205°C.

[Elemental analysis:- C,54.6;H,3.99;N,5.28%;
Calculated:- C,54.3;H,3.80;N,5.28%].

AW (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{3-methylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 86-88°C.

[Elemental analysis:- C,67.90;H,6.40;N,6.50;S,7.30%;
Calculated:- C,68.22;H,6.20;N,6.63;S,7.59%].

AX (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{4-methylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 205-7°C.

[Elemental analysis:- C,68.1;H,6.09;N,6.42%;
Calculated:- C,68.22;H,6.20;N,6.63%].

AY (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{4-isopropylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 89-91°C.

[Elemental analysis:- C,69.8;H,7.2;N,5.9;S,6.36%;
Calculated:- C,70.26;H,7.16;N,5.85;S,6.69%.

AZ (4R,4S)(6R,6S)-6-[(4,5-Bis{4-tertbutylphenyl}-imidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one, m.p. 134-51°C.
[Elemental analysis ($C_{30}H_{38}N_2O_3S$:1/4H_2O):-
C,70.5;H,7.7;N,5.3;S,6.33;H_2O,1.2%;
Calculated:- C,70.48;H,7.59;N,5.48;S,6.2;H_2O,0.81%].

BA (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{2-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 108-10°C.
[Elemental analysis ($C_{24}H_{26}N_2O_5S$:$C_4H_8O_2$):-
C,61.8;H,5.9;N,5.5;S,6.37%;
Calculated:- C,61.99;H,6.27;N,5.17;S,5.90%].

BB (4R,4S)(6R,6S)-4-Hydroxy-6-[(4,5-bis{3-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 148°C.
[Elemental analysis ($C_{24}H_{26}N_2O_5S$:0.45$C_4H_8O_2$):-
C,62.2;H,5.74;N,5.79%;
Calculated:- C,62.7;H,6.04;N,5.67;S,6.94%].

BC & BD

BC By proceeding in a similar manner, and replacing the 4,5-bis(3-chlorophenyl)imidazole-2-thiol by 4,5-diphenylimidazole-2-thiol in the reaction with t-butyl-5,6-epoxy-3-hydroxy-3-methylhexanoate, there was obtained a product in the form of a mixture of 2

racemates. This mixture was triturated with diethyl ether, and the insoluble material recrystallised from a mixture of ethyl acetate and methanol, to give 6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one, m.p. 201-202.5°C.
[Elemental analysis:- C,67.10;H,5.70;N,7.10;S,8.00%;
Calculated:- C,66.98;H,5.62;N,7.10;S,8.13%.
NMR (in CD_3SOCD_3):- 1.1(3H,s), 1.64-2.06(2H,m), 2.3-2.6(2H,m), 3.4-3.5(2H,m), 4.76-4-92(1H,m), 5.06(1H,m)].

BD The washings from the trituration were concentrated, to give a white solid, which was recrystallised from a mixture of ethyl acetate and methanol, to give 6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one, m.p. 203.5-205°C.
[Elemental analysis:- C,66.60;H,5.56;N,6.94;S,8.10%;
Calculated:- C,66.98;H,5.62;N,7.10;S,8.13%.
NMR (in CD_3SOCD_3):- 1.24(3H,s), 1.7-2.3(2H,m), 2.3-2.7(2H,m), 3.4-3.5(2H,m), 4.54-4.7(1H,m), 5.04(1H,s), 7.15-7.6(10H,m)].

BE & BF By proceeding in a similar manner to that described for Compounds BC and BD, but replacing the 4,5-diphenylimidazole-2-thiol by the appropriate quantity of 4,5-bis-(4-methoxyphenyl)imidazole-2-thiol, there were obtained:-

4-hydroxy-6-[(4,5-bis{4-methoxyphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one, m.p. 214-215° and 90-115°C. [Elemental analyses:- Compound BE:- C,63.3;H,5.82;N,6.11;S,7.1%; Compound BF:- C,63.8;H,5.94;N,5.94;S,6.9%; Calculated:- C,63.44; H,5.73;N,6.17;S,7.05%].

EXAMPLE 15

Compounds BG TO BL

BG A suspension of (4R,4S)(6R,6S)-4-hydroxy-6-[(4,5-bis{4-methylphenyl}imidazol-2-yl)thiomethyl]-4-methyltetrahydropyran-2-one (4.7g.) in dichloromethane (250ml) was treated dropwise with trifluoroacetic anhydride (6.3g) with ice-cooling, and left to stand at room temperature for 24 hours. The resulting solution was washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate, and evaporated, to give a gum. This gum was dissolved in toluene (200ml), and treated with 1,8-diazabicyclo[5.4.0]undec-2-ene (4.5g), and left to stand at room temperature for 24 hours. The solution was then washed with water, dried over magnesium sulphate, and evaporated to give a white foam. This was recrystallised from a mixture of ethyl acetate and methanol, to give (6R,6S)-6-[(4,5-bis{4-methylphenyl}-imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one, (2.1g), m.p. 191°C.

[Elemental analysis:- C,71.2;H,6.12;N,6.85;S, 7.8 %; Calculated:- C,71.26;H,5.98;N,6.93;S,7.93%. NMR (in $CDCl_3$):- 1.96(3H,s), 2.3(6H,s), 2.54(2H,d,J = 8Hz), 3 .48(2H,d,J = 6Hz), 4.6-4.8(1H,m), 5.8(1H,d), 7.0-7.2(8H,m).

By proceeding in a similar manner, but replacing compound AX with the appropriate quantity of the corresponding compound from compounds AR to BF, there were also prepared:-

BH (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)-thiomethyl]-5,6-dihydro-4-methylpyran-2-one, m.p. 70-71°C. [Elemental analysis:- C, 69.7;H,5.69;N,7.3;S,8.6%; Calculated:- C,70.19;H,5.36;N,7.44;S,8.52%].

BI (6R,6S)-6-[(4,5-Bis{4-chlorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one, m.p. 175-176°C. [Elemental analysis:- C,59.1;H,4.04;N,6.3;S,7.3;Cl,15.8%; Calculated:- C,59.33;H,4.07;N,6.29;S,7.20;Cl,15.92%].

BJ (6R,6S)-6-[(4,5-bis{3-chlorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one, m.p. 132-135°C.

[Elemental analysis:- C,59.3;H,4.2;N,6.4;S,7.1;Cl,15.6%; Calculated:- C,59.33;H,4.07;N,6.29;S,7.20;Cl,15.92%].

BK (6R,6S)-6-[(4,5-bis-{2-chlorophenyl}imidazol-

2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one, m.p.. 126-127°C.

[Elemental analysis:- C,59.2;H,4.04;N,6.2;Cl,15.9%; Calculated:- C,59.33;H,4.07;N,6.29;S,7.20;Cl,15.92%].

BL (6R,6S)-6-[(4,5-bis-{4-fluorophenyl}imidazol-2-yl)thiomethyl]-5,6-dihydro-4-methylpyran-2-one, m.p. 123-126°C.

[Elemental analysis:- C,64.5;H,4.6;N,6.9;S,7.8;F,9.3%; Calculated:- C,64.06;H,4.4;N,6.79;S,7.77;F,9.21%].

EXAMPLE 16

Compounds BM TO BQ

BM A mixture of 5-(iodomethyl)-2-furanone (2.06g), 4,5-bis-(4-methylphenyl)imidazole-2-thiol (2.29g), and potassium carbonate (0.56g), in dry dimethylformamide (40ml) was stirred at room temperature for 24 hours. The dimethylformamide was removed by evaporation at reduced pressure, and the residue was shaken with water and dichloromethane, the organic layer separated, and the aqueous layer extracted with more dichloromethane. The combined organic solutions were dried over magnesium sulphate and concentrated, to give a yellow semi-solid. This was subjected to chromatography on silica gel, eluting with a mixture of ethyl acetate and dichloromethane, (3:7v/v), and the foam obtained was recrystallised from diethyl ether to give (5R,5S)-5-[(4,5-bis-{4-methylphenyl}imidazol-2-

yl)thiomethyl]tetrahydrofuran-2-one, (2.05g), m.p. 128-129°C.

[Elemental analysis:- C,69.7;H,5.83;N,7.3;S,8.6%; Calculated:- C,69.81;H,5.86;N,7.40;S,8.47%.

NMR (in $CDCl_3$):- 1.96-2.7(4H,m), 2.36(6H,s), 3.3(2H,dd,J = 6Hz,2HZ), 4.72-4.9(1H,m), 6.96-7.5(8H,m)].

BN By proceeding in a similar manner, but replacing the 4,5-bis-(4-methylphenyl)imidazole-2-thiol by the appropriate quantity of 4,5-diphenylimidazole-2-thiol, and the 5-(iodomethyl)-2-furanone by the appropriate quantity of (6R,6S)-6-(iodomethyl)-3,4,5,6-tetrahydropyran-2-one, there was prepared:- (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-3,4,5,6-tetrahydropyran-2-one, with no sharp melting point.

[Elemental analysis:- C,69.00;H,5.52;N,7.7;S,8.70%; Calculated:- C,69.20;H,5.53;N,7.69;S,8.80].

BO By again proceeding in a similar manner, but replacing the (6R,6S)-6-(iodomethyl)-3,4,5,6-tetrahydropyran-2-one by 4,4-dimethyl-6-iodomethyl-3,4,5,6-tetrahydropyran-2-one there was prepared:- (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4,4-dimethyl-3,4,5,6-tetrahydropyran-2-one, m.p. 130-131°C.

[Elemental analysis:- C,70.0;H,6.34;N,6.6;S,8.1%;

Calculated:- C,70.38;H,6.16;N,7.14;S,8.17%.

By again proceeding in a similar manner, but replacing the 5-(iodomethyl)-2-furanone by (4R,4S)(6R,6S)-4-hydroxy-6-iodomethylpyran-2-one, there was obtained, after chromatography:-

BP (4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-3,4,5,6-tetrahydropyran-2-one, m.p. 191-192°C.

[Elemental analysis:- C,66.2;H,5.26;N,7.3;S,8.2%; Calculated:- C,66.29;H,5.30;N,7.36;S,8.43%] and

BQ (3R,3S)(5R,5S)-ethyl 6-[(4,5-diphenylimidazol-2-yl)thio]-3,5-dihydroxyhexanoate, m.p. 94-95°C.

[Elemental analysis:- C,64.4;H,6.02;N,6.48;S,7.5 %; Calculated:- C,64.77;H,6.14;N,6.57;S,7.52%].

NMR (in $CDCl_3$):- 1.21(3H,t), 1.5-2.1(2H,m), 2.22-2.6(2H,m), 2.9-3.2(2H,m), 4.16(2H,q), 2.2-2.4(2H,m).

EXAMPLE 17

Compound BR

A mixture of 4,5-diphenylimidazole-2-thiol (3.5g) and anhydrous potassium carbonate (2.9g) in anhydrous dimethylformamide (60ml) was stirred at room temperature for 30 minutes. It was then treated with (2R,2S)-2-(iodomethyl)-6-oxo-1,4-dioxane (3.4g) and the resulting mixture stirred at room temperature for 3 days. The mixture was poured into water (600ml) and the product collected by filtration and dried at

60°C., to give a cream solid (2.6g). A portion (1.5g) of this solid was dissolved in dichloromethane (60ml) and treated with trifluoroacetic acid (0.48g). After 30 minutes the solution was diluted with fresh dichloromethane (100ml) and washed with 5% sodium hydrogen carbonate solution (75ml). The layers were separated and the organic fraction washed with water (50ml), dried (magnesium sulphate) and evaporated. Crystallisation from tetrahydrofuran/diethyl ether gave (6R,6S)-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-oxo-1,4-dioxane (0.5g) in the form of a white powder, m.p. 194-196°C.

[Elemental analysis:- C,64.8;H,4.91;N,7.7;S,8.8%;
Calculated:- C,65.57;H,4.92;N,7.65;S,8.74%;
NMR (CD_3SOCD_3):- 3.46 (2H,d,J = 6Hz), 3.76 (1H,dd,J = 12Hz, 6Hz), 4.05 (1H,dd,J = 12Hz, 4Hz), 4.32 (2H,dd,J = 16Hz, 4Hz), 4.87 (1H,m), 7.2-7.5 (10H,m)].

EXAMPLE 18

Compound BS

Sodium methoxide (0.34g) was added to a suspension of 4,5-bis-(4-chlorophenyl)imidazole-2-thiol (2.0g) in methanol (50ml), and the mixture was stirred at room temperature for one hour. t-Butyl 5,6-epoxy-3-hydroxy-3-methylhexanoate (1.98g), was added and the mixture was stirred at room temperature for 18 hours. It was then concentrated at reduced pressure and the

residue was shaken with ethyl acetate and water. The ethyl acetate layer was separated, dried over magnesium sulphate, and concentrated, to give a semi-solid. This was triturated with diethyl ether, to give a white solid, which was subjected to chromatography on silica gel eluting with a mixture of dichloromethane and ethyl acetate, to give a gum, which was recrystallised from cyclohexane to give t-butyl 6-[(4,5-bis-{4-chloro-phenyl}imidazol-2-yl)thio]-3,5-dihydroxy-3-methyl-hexanoate in the form of one racemate, a white crystalline solid, m.p. 152-153°C. [Elemental analysis:- C,58.3;H,5.68;Cl,13.3;N,5.18;S,5.94%; Calculated:- C,58.1;H,5.63;Cl,13.19;N,5.21;S,5.97%. NMR (in $CDCl_3$):- 1.32(3H,s), 1.46(9H,s), 1.64 (1H,dd,J = 12Hz, 4Hz), 1.9-2.1(1H,m), 2.3-2.7(2H,m), 2.98-3.3(2H,m), 4.3-4.5(1H,m), 4.8-6.4(2H,br.s), 7.1-7.6(8H,m).

EXAMPLE 19

Compound BT

6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one (4.22g), was added to a solution of sodium hydroxide (1.0M;10.66ml) and water (70ml), and warmed at 60°C for 10 minutes. Traces of solid were removed by filtration, and the filtrate was concentrated at reduced pressure to give a glass. This was dissolved in dimethylformamide (40ml),

and treated with ethyl iodide (2.15g), and the mixture was stirred at room temperature for 2 hours. It was then shaken with ethyl acetate and water, the organic layer was separated and washed with water, dried over magnesium sulphate, and concentrated, to give an oil. This was subjected to chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:1v/v), to give (3R,3S)(5R,5S)-ethyl 6-[(4,5-diphenylimidazol-2-yl)thio]-3,5-dihydroxy-3-methylhexanoate (2.47g), in the form of a yellow solid with no sharp melting point.

[Elemental analysis:- C,64.9;H,6.4;N,6.2;S,7.1%; Calculated:- C,64.46;H,6.54;N,6.54;S,7.48%.

NMR (in $CDCl_3$):- 1.24(3H,2dt), 1.6(1H,dd,J = 10Hz, 3Hz), 1.9-2.1(1H,m), 2.4-2.7(1H,m), 2.9-3.2(2H,m), 4.05-4.24 (3H,m), 4.38-4.58(1H,m), 7.1-7.5(10H,m)].

EXAMPLE 20

Compound BU

(6R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thio-methyl]-4,4-dimethyl-3,4,5,6-tetrahydropyran-2-one (1.18g) was dissolved in 33% ethanolic methylamine (50ml), and heated at reflux for 2 hours. It was then concentrated to give a solid, which was recrystallised from ethanol to give (2R,2S)-2-[(2-hydroxy-4,4-dimethyl-5-methylaminocarbonylpent-1-yl)thio]-4,5-diphenylimidazole (0.53g), m.p. 190-191°C.

[Elemental analysis:- C,68.3;H,7.0;N,9.9;S,8.1%;
Calculated:- C,68.05;H,6.9;N,9.92;S,7.6%.
NMR (in CD_3SOCD_3) 0.98(3H,s), 1.0(3H.s), 1.5-1.7(2H,m), 1.98-2.24(2H,m), 2.5-2.7(4H,m), 3.18(2H,m), 3.9-4.05(1H,m), 5.5-5.7(1H,m), 7.2-7.9(10H,m)].

EXAMPLE 21

Compounds BV and BW

BV (6R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-3,4,5,6-tetrahydropyran-2-one, (3.96g), in dry tetrahydrofuran, (55ml), was treated at -78°C in an argon atmosphere with di-isobutylaluminium hydride in tetrahydrofuran (1.0M;55ml), and stirred at -78°C for 3 hours. It was then poured into a mixture of ice (250g), water (100ml) and acetic acid (50ml), and extracted with dichloromethane. The dichloromethane extracts were combined, washed with water, and dried over magnesium sulphate. Concentration gave a yellow oil, which was subjected to chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (3:1v/v), and the white solid obtained was recrystallised from a mixture of ethyl acetate and hexane to give (2R,2S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-hydroxy-3,4,5,6-tetrahydropyran (1.15g), m.p.. 172-173°C.
[Elemental analysis:- C,68.7;H,6.03;N,7.6;S,8.5%;
Calculated:- C,68.82;H,6.05;N,7.64;S,8.75%.

NMR (in a mixture of $CDCl_3$ and CD_3SOCD_3):- 1.2-2.1(6H,m), 2.9-3.3(2H,m), 3.6-3.8(1/4H,m), 4.1-4.3(3/4H,m), 4.7-4.8(1/4H,m), 5.34(3/4H,s), 5.78(3/4H,d,J = 3Hz), 6.46(1/4H,d,J = 6Hz), 7.1-7.8(10H,m)].

BW By proceeding in a similar manner, but replacing (6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-3,4,5,6-tetrahydropyran-2-one by 6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-4-methyltetrahydropyran-2-one there was prepared (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2,4-dihydroxy-4-methyltetrahydropyran, m.p. 134-151°C.

[Elemental analysis:- C,66.8;H,6.11;N,7.2;S,8.1%; Calculated:- C,66.64;H,6.10;N,7.07;S,8.09%].

EXAMPLE 22

Compounds BX & BY

(2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2,4-dihydroxy-4-methyltetrahydropyran (1.9g), was dissolved in anhydrous methanol (150ml), boron trifluoride diethyl etherate (3ml) was added, and the solution was left to stand at room temperature for 64 hours. It was then added to excess sodium bicarbonate solution, extracted with ethyl acetate, and the organic extracts were washed with water, dried over magnesium sulphate, and concentrated, to give a white

solid. This was subjected to chromatography on silica gel eluting with a mixture of ethyl acetate and cyclohexane (2:1v/v), to give compound BX, (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-4-methyltetrahydropyran (0.61g), thought to be the 2-alpha-anomer, in the form of a white solid, m.p. 163-166°C.
[Elemental analysis:- C,67.1;H,6.41;N,6.61;S,7.6%;
Calculated:- C,67.29;H,6.38;N,6.83;S,7.81%.
NMR (in CD_3SOCD_3):- 1.16(3H,s), 1.1-1.4(2H,m), 1.5-1.7(2H,m), 3.3(3H,s), 3.2-3.4(2H,m), 3.9-4.1(1H,m), 4.48(1H,s), 4.58(1H,dd,J = 6Hz,2Hz); and
compound BY, (2R,2S)(4R,4S)(6R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethy]-4-hydroxy-2-methoxy-4-methyltetrahydropyran, thought to be the the 2-beta-anomer, 0.51g, m.p. 46°C.
[Elemental analysis:- C,67.1;H,6.68;N,6.52;S,7.4%;
Calculated:- C,67.29;H,6.38;N,6.83;S,7.81%.
NMR (in CD_3SOCD_3)- 1.08(1H,s), 1.25-1.75(4H,m), 3.3(3H,m), 3.2-3.4(2H,m), 4.0(1H,s), 4.1-4.22(1H,m), 4.8(1H,m), 7.1-7.5(10H,m)].

EXAMPLE 23

Compound BZ

4,5-diphenylimidazole-2-thiol (12.99g) was dissolved in dry dimethylformamide (200ml), and then it was treated with potassium carbonate (5.44g) and methyl

6-deoxy-6-iodo-A-D-mannopyranoside (15.66g) and stirred at room temperature for 18 hours. The mixture was then filtered and concentrated at reduced pressure to give an orange oil, which was subjected to chromatography on silica gel, eluting with a mixture of ethyl acetate and hexane,(9:1v/v), to give a white solid which was triturated with cyclohexane to give (2S,3R,4R,5S,6S)-2-[(4,5-diphenylimidazol-2-yl)thiomethyl]-6-methoxy-3,4,5-trihydroxytetrahydropyran (7.0g), m.p. 120-122°C.

[Elemental analysis:- C,61.2;H,5.87;N,6.44;S,8.0%;

Calculated:- C,61.66;H,5.65;N,6.54;S,7.48%.

NMR (in $CDCl_3$):- 3.34(3H,m), 3.4-4.1(6H,m), 4.7(1H,s), 7.2-7.5(10H,m).

EXAMPLE 24

Compounds CA to CF

CA A solution of 1-methylimidazole (5.0g) in tetrahydrofuran (70ml) was treated with a solution of lithium diisopropylamide mono-tetrahydrofuran complex in cyclohexane (40ml;1.5M) during 10 minutes under nitrogen, keeping the temperature between -60° and -30°C. The solution was then stirred for 30 minutes, warming to 10°C. The solution was then cooled to -20°C and treated with a solution of 4-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]morpholine (6.15g) in a mixture of tetrahydrofuran (50ml) and 1,4-dioxane (50ml). The solution was stirred at ambient temperature for 6 hours, and then it was treated with dilute hydrochloric acid (100ml;2N) and the aqueous layer was separated. The organic fraction was extracted with water (100ml), the combined aqueous layers were washed with t-butyl methyl ether (100ml), then basified with aqueous sodium hydroxide solution (120ml;2N) and extracted with t-butyl methyl ether (3x200ml). The ether solution was washed with aqueous sodium chloride solution and concentrated under reduced pressure to leave a solid. The solid was recrystallised from methanol, to give 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methyl-

imidazole (4.0g) in the form of a white powder, m.p. 160-163°C.

CB By proceeding in a similar manner to that described above but replacing the 4-[4-(4,5-diphenyl-imidazol-2-ylthio)butanoyl]morpholine by 4-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-morpholine there was prepared 2-[5-(4,5-diphenylimid-azol-2-ylthio)pentanoyl]-1-methylimidazole, in the form of a white solid, m.p. 121-123°C, after chromatography on silica gel, eluting with ethyl acetate.

CC By proceeding in a similar manner to that described above but replacing the 4-[4-(4,5-diphenyl-imidazol-2-ylthio)butanoyl]morpholine by 4-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]morpholine there was prepared 2-[6-(4,5-diphenylimidazol-2-yl-thio)hexanoyl]-1-methylimidazole, in the form of a white solid, m.p. 124-126°C, after chromatography on silica gel, eluting with ethyl acetate.

CD By proceeding in a similar manner to that described above but replacing the 1-methylimidazole by 1-[(dimethylamino)methyl]imidazole, there was prepared 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]imidazole, in the form of a white solid, m.p. 186-188°C, from acetonitrile.

CE By proceeding in a similar manner to that described above but replacing the 1-methylimidazole by

1-[(dimethylamino)methyl]imidazole and replacing the 4-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]morpholine by 4-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]-morpholine, there was prepared 2-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]imidazole, m.p. 148-152°C, from butan-2-one.

CF By proceeding in a similar manner to that described above but replacing the 1-methylimidazole by 1-[(dimethylamino)methyl]imidazole and replacing the 4-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]morpholine by 4-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-morpholine, there was prepared 2-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]imidazole, in the form of a white powder, m.p. 188-191°C, from butan-2-one.

EXAMPLE 25

Compounds CG to CL

CG A suspension of 2-[4-(4,5-diphenylimidazol-2--ylthio)butanoyl]-1-methylimidazole (2.0g) in ethanol was treated with a solution of sodium borohydride (0.96g) in water (25ml). The mixture was heated at reflux for 1 hour, filtered, and treated with acetone (25ml), followed by dilute hydrochloric acid (200ml; 1N). The pH was adjusted to 7 and the mixture was extracted with t-butyl methyl ether (3x150ml), then dried and concentrated under reduced pressure to leave an oil. Chromatography on silica gel, eluting with a

mixture of ethyl acetate and methanol, gave 2-[4-(4,5-diphenylimidazol-2-ylthio)-1-hydroxybutyl]-1-methylimidazole (1.32g) in the form of a glass [NMR ($CDCl_3$):- 1.78 (2H,m), 2.09 (2H,m), 2.97 (2H,m), 3.58 (3H,s), 4.83 (1H,dd,J=5Hz & 7Hz), 6.56 (1H,d, J=2Hz), 6.68 (1H,d,J=2Hz), 7.19-7.27 (6H,m), 7.40-7.45 (4H,m)].

CH By proceeding in a similar manner to that described above but replacing the 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methylimidazole by 2-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]-1-methylimidazole, there was prepared 2-[6-(4,5-diphenylimidazol-2-ylthio)-1-hydroxyhexyl]-1-methylimidazole in the form of a glass. [Elemental analysis:- C,69.4; H,6.57;N,12.9;S,7.3%; calculated:- C,69.41;H,6.52; N,12.95;S,7.41%].

CI By proceeding in a similar manner to that described above but replacing the 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methylimidazole by 2-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-1-methylimidazole there was prepared 2-[5-(4,5-diphenylimidazol-2-ylthio)-1-hydroxypentyl]-1-methylimidazole in the form of a glass. [Elemental analysis:- C,67.3;H,6.27;N,12.6;S,7.4%; calculated for $C_{24}H_{26}N_4OS:0.5H_2O$:- C,7.42;H,6.37;N,13.10;S,7.50%].

CJ By proceeding in a similar manner to that described above but replacing the 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methylimidazole by 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]imidazole there was prepared 2-[4-(4,5-diphenylimidazol-2-ylthio)-1-hydroxybutyl]imidazole in the form of a glass. [Elemental analysis:- C,65.1;H,5.71;N,13.4;S,7.6%; calculated for $C_{22}H_{22}N_4OS:H_2O$:- C,64.68;H,5.92;N,13.71; S,7.85%. NMR ($CDCl_3$):- 1.56 (1H,m), 1.66 (1H,m), 1.83 (1H,m), 2.00 (1H,m), 2.71 (1H,m), 2.88 (1H,m), 4.92 (1H,bt,w1/2 = 16Hz), 6.64 (2H,s), 7.12-7.22 (6H,m), 7.33-7.40 (4H,m)].

CK By proceeding in a similar manner to that described above but replacing the 2-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]-1-methylimidazole by 2-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]imidazole there was prepared 2-[5-(4,5-diphenylimidazol-2-ylthio)-1-hydroxypentyl]imidazole in the form of a glass. [Elemental analysis:- C,62.8;H,5.85;N,12.7;S,7.3%; calculated for $C_{23}H_{24}N_4OS:2H_2O$:- C,62.70;H;6.41; N,12.72;S,7.28%. NMR ($CDCl_3$):- 1.52 (2H,m), 1.63 (2H,m), 1.94 (1H,m), 2.08 (1H,m), 2.90 (1H,m), 3.06 (1H,m), 5.08 (1H,t,J = 6Hz), 6.08 (2H,s), 7.18-7.30 (6H,m), 7.42 (4H,dd,J = 7Hz & 2Hz)].

CL By proceeding in a similar manner to that described above but replacing the 2-[4-(4,5-diphenyl-

imidazol-2-ylthio)butanoyl]-1-methylimidazole by 2-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]imidazole there was prepared 2-[6-(4,5-diphenylimidazol-2-ylthio)-1-hydroxyhexyl]imidazole in the form of a glass. NMR ($CDCl_3$):- 1.38-1.53 (4H,m), 1.71 (2H,p,J = 7Hz), 1.81 (1H,m), 1.89 (1H,m), 3.08 (2H,m), 4.75 (1H,dd,J = 7Hz & 5Hz), 6.90 (2H,s), 7.20-7.32 (6H,m), 7.48 (4H,dd, J = 8Hz & 2Hz), 7.63 (1H,s)].

EXAMPLE 26

Compound CM

A solution of morpholine (6.0g) and pyridine (5.6g) in dimethylformamide (10ml) was added during 10 minutes to a stirred solution of 4-chlorobutyryl chloride (9.4g) in dimethylformamide (100ml). The mixture was stirred at ambient temperature for 2 hours and then it was treated with 4,5-diphenylimidazole-2-thiol (15.0g). The mixture was stirred at 125-135°C for 4 hours. After cooling to room temperature, the mixture was poured into dilute aqueous potassium carbonate solution (1 litre) to give a sticky solid. This solid was dissolved in dichloromethane (1 litre), was the resulting solution was washed with water (2x500ml) and dried by filtering through anhydrous sodium sulphate. Concentrating under reduced pressure gave a thick brown oil, which was partitioned between hydrochloric acid (300ml;1N) and toluene (300ml).

The toluene fraction was extracted with hydrochloric acid (200ml;1N) and the combined acidic solution was adjusted to pH4 by treatment with sodium acetate, and was then extracted with toluene (3x200ml). This toluene solution was washed with brine, dried over magnesium sulphate and concentrated under reduced pressure to give a solid. The solid was crystallised from a mixture of t-butyl methyl ether (300ml) and ethanol (150ml) by concentrating to about 200ml and cooling overnight, to give 4-[4-(4,5-diphenylimidazol-2-ylthio)butanoyl]morpholine (10.92g) in the form of colourless crystals, m.p. 168-173°C.

EXAMPLE 27

Compound CN

A solution of morpholine (13.0g) and pyridine (13.0g) in dimethylformamide (50ml) was added during 10 minutes to a stirred solution of 5-chlorovaleryl chloride (22.0g) in dimethylformamide (150ml). The mixture was stirred at ambient temperature for 2 hours then 4,5-diphenylimidazole-2-thiol (37.0g) was added. The mixture was stirred at 125-135°C for 2 hours. After cooling to 80°C, the mixture was poured into water (500ml) and acidified to pH1 by treatment with dilute hydrochloric acid . The mixture was stirred and the resulting solid was filtered off. The filtrate was adjusted to pH4 by treatment with sodium acetate,

to give a sticky solid. This solid was dissolved in dichloromethane (1 litre), was washed with water (500ml), and then dried over magnesium sulphate and concentrated under reduced pressure, to give an oil. The oil was crystallised from t-butyl methyl ether, to give 4-[5-(4,5-diphenylimidazol-2-ylthio)pentanoyl]-morpholine (43.8g), in the form of a white powder, m.p. 134-136°C.

EXAMPLE 28

Compound CO

A solution of 6-(4,5-diphenylimidazol-2-ylthio)-hexanoyl chloride [prepared from 6-(4,5-diphenylimid-azol-2-ylthio)hexanoic acid (11.5g) and thionyl chloride] in dichloromethane (50ml) was added dropwise to a solution of morpholine (6.0g) in dichloromethane (150ml), keeping the temperature below 30°C. The mixture was stirred at ambient temperature for 2 hours and was then left overnight. The mixture was washed with hydrochloric acid (100ml;1N), water (100ml), aqueous potassium hydroxide solution (100ml;1N) and with brine (2x50ml), and was then dried over magnesium sulphate. Concentrating under reduced pressure gave a gum, which was triturated with diethyl ether to give 4-[6-(4,5-diphenylimidazol-2-ylthio)hexanoyl]morpholine (9.64g) in the form of an off-white solid, m.p. 120-122°C.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also

include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Compositions according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I or a pharmaceutically acceptable salt thereof.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The size and frequency of the dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration, the duration of the treatment and the age, sex, size and condition of the patient. In the adult, the doses are generally from 0.01 to 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from 0.001 to 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration.

The following Example illustrates a pharmaceutical composition according to the present invention.

COMPOSITION EXAMPLE

No. 2 size gelatin capsules each containing:-

Compound A	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

were prepared in accordance with the usual procedure.

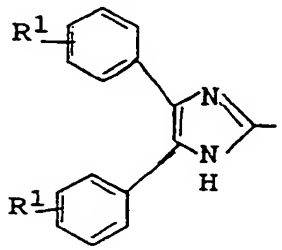
Capsules can also be made up in a similar manner using any other of the compounds B to CO, or a pharmaceutically acceptable salt thereof.

CLAIMS

1. An imidazole derivative of the general formula I:

$$A\text{-}S(O)_k\text{-}Q\text{-}Z \qquad (I)$$

wherein A represents a group of general formula (II):



(II)

wherein the symbols R^1 may be the same or different and each represents hydrogen or one or more substituents,

k represents 0, 1 or 2;

Q represents a methylene group or alkylene chain containing from 2 to 5 carbon atoms, optionally substituted with one or more alkyl groups containing from 1 to 4 carbon atoms; and

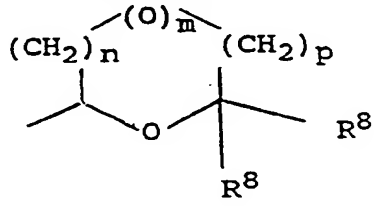
Z represents a hydrogen atom; a hydroxy group; an optionally substituted alkoxy group; an optionally substituted aryl group; a dialkylamino group wherein the alkyl groups may be the same or different and each is straight- or branched-chain and contains from 1 to 4 carbon atoms; a group of the formula $-NHR^2$, wherein R^2 represents an acyl group, a group of the formula $-C(SR^3)=N-CN$ wherein R^3 represents a straight- or branched-chain alkyl group containing from 1 to 3 carbon atoms, or R^2 represents a 5- or 6-membered nitrogen-containing heterocyclic ring

optionally substituted by one or more substituents; or

Z represents a group of the formula $-COR^4$ wherein R^4 represents a straight- or branched-chain alkyl group containing from 1 to 3 carbon atoms; a group of the formula $-CH(OH)R^5$, $-COR^5$, $-CSR^5$, $-CONHR^5$ or $-CSNHR^5$ wherein R^5 represents a 5- or 6-membered nitrogen-containing heterocyclic ring which may also contain an oxygen atom, optionally substituted by one or more substituents; an alkynyl or cycloalkyl group containing up to 6 carbon atoms; a group of the formula $-CH(R^6)OR^7$ wherein R^6 represents a straight- or branched-chain alkenyl or alkoxy group containing up to 6 carbon atoms and R^7 represents a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, optionally substituted by one or more substituents;

or Z represents:

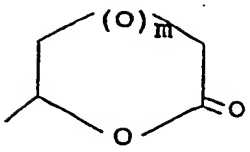
a group of the general formula (III)



(III)

wherein m is 0 or 1, n is 0 or 1 and p is 1, 2 or 3, and the symbols R^8 each represent a hydrogen atom, or a methyl group substituted by a straight- or branched-chain alkoxy or alkanoyloxy group containing up to 6 carbon atoms;

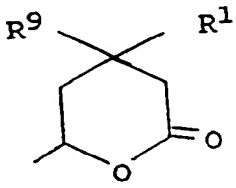
a group of the general formula (IV)



(IV)

wherein m is as hereinbefore defined;

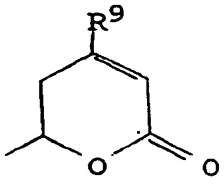
a group of the general formula (V)



(V)

wherein R^9 represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms and R^{10} represents a hydrogen atom, a hydroxy group or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms;

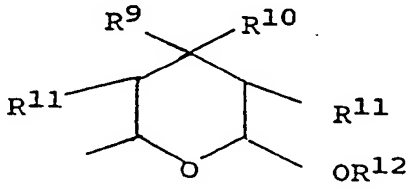
a group of the general formula (VI)



(VI)

wherein R^9 is as hereinbefore defined;

a group of the general formula (VII)



(VII)

wherein R^9 and R^{10} are as hereinbefore defined, the symbols

R^{11} may be the same or different and each represents a hydrogen atom or a hydroxy group and R^{12} represents a hydrogen atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms;

or a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2-COR^{13}$ wherein R^9 and R^{10} are as hereinbefore defined, r represents 0 or 1 and R^{13} represents a hydroxy group or a straight- or branched-chain alkoxy or alkylamino group containing from 1 to 4 carbon atoms;

with the exclusion of (2S, 4R, 6S)-6-[4,5-diphenylimidazol-2-yl)-thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran and (2R, 4R, 6S)-6-[4,5-diphenylimidazol-2-yl)-thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, in which, in the group A, the symbols R^1 may be the same or different and each represents hydrogen or one or more substituents selected from halogen atoms, and straight- or branched-chain alkyl and alkoxy groups containing from 1 to 6 carbon atoms, and trifluoromethyl groups.

3. A compound according to claim 1 or 2, in which Z represents a hydrogen atom; a hydroxy group; an alkoxy group containing 1 to 6 carbon atoms optionally substituted by an alkoxy or alkoxyalkoxy group containing 1 to 6 carbon atoms in each alkoxy moiety; an aryl group optionally substituted by one or more alkoxy groups

containing 1 to 6 carbon atoms; a dialkylamino group wherein the alkyl groups may be the same or different and each is straight- or branched-chain and contains from 1 to 4 carbon atoms; a group of the formula $-NHR^2$, wherein R^2 represents a straight- or branched-chain alkanoyl group containing up to 6 carbon atoms and which is optionally substituted by a carboxy group, or R^2 represents a group of the formula $-C(SR^3)=N-CN$ wherein R^3 represents a straight- or branched-chain alkyl group containing from 1 to 3 carbon atoms, or R^2 represents a 5- or 6-membered nitrogen-containing heterocyclic ring optionally substituted by one or more substituents selected from amino groups and straight- or branched-chain alkyl groups containing from 1 to 3 carbon atoms; and attached to the group NH via a carbon atoms; or Z represents a group of the formula $-COR^4$ wherein R^4 represents a straight- or branched-chain alkyl group containing from 1 to 3 carbon atoms; a group of the formula $-CH(OH)R^5$, $-COR^5$, $-CSR^5$, $-CONHR^5$ or $CSNHR^5$ wherein R^5 represents a 5- or 6-membered nitrogen-containing heterocyclic ring which may also contain an oxygen atom, optionally substituted by one or more substituents selected from straight- or branched-chain alkyl groups containing from 1 to 3 carbon atoms; and alkynyl or cycloalkyl group containing up to 6 carbon atoms; a group of the formula $-CH(R^6)OR^7$ wherein R^6 represents a straight- or branched-chain alkenyl or alkoxy group containing up to 6 carbon atoms and R^7 represents a straight- or branched-chain alkyl

group containing from 1 to 4 carbon atoms, optionally substituted by one or more substituents selected from hydroxy groups; a group of the general formula (III), (IV), (V), (VI), or (VII) as hereinbefore defined; or a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{13}$ as hereinbefore defined.

4. A compound according to any one of the preceding claims in which:

(i) in the group A, the symbols R^1 may be different or the same and each represents a hydrogen, chlorine or fluorine atom or a straight- or branched-chain alkyl group containing from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy group containing from 1 to 3 carbon atoms, or a trifluoromethyl group;

(ii) k represents 0;

(iii) Z represents a hydrogen atom; a hydroxy group; an ethoxy group optionally substituted by a methoxyethoxy group; a phenyl group optionally substituted by one or more alkoxy groups; a dialkylamino group wherein the alkyl groups may be the same or different and each is straight- or branched-chain and contains from 1 to 3 carbon atoms; an ethynyl group, or a cyclohexyl group;

(iv) Z represents a group $-NHR^2$, in which R^2 represents a straight- or branched chain alkanoyl group containing up to 6 carbon atoms optionally substituted by a carboxy group; a pyridyl or triazolyl group optionally substituted by one or two substituents selected from amino

groups and straight- or branched-chain alkyl groups;

(v) Z represents a group $-NHC(SR^3)=N-CN$, wherein R^3 represents a methyl group;

(vi) Z represents a group $-COR^4$ wherein R^4 represents a methyl group;

(vii) Z represents a group $-CH(OH)R^5$, $-COR^5$, $-CSR^5$, $-CONHR^5$ or $-CSNHR^5$ wherein R^5 represents a imidazolyl, morpholinyl or pyridyl group optionally substituted by one or two alkyl groups;

(viii) Z represents a group $-CH(R^6)OR^7$, wherein R^6 represents an allyl group, or an alkoxy group containing from 1 to 3 carbon atoms;

(ix) Z represents a group $-CH(R^6)OR^7$, wherein R^7 represents an alkyl group containing from 1 to 3 carbon atoms, optionally substituted by a hydroxy group;

(x) Z represents a group of formula (III), in which R^8 represents a hydrogen atom or a hydroxymethyl, methoxymethyl or acetoxymethyl group;

(xi) Z represents a group of formula (V), (VI) or (VII), in which R^9 represents a hydrogen atom or a methyl group;

(xii) Z represents a group of formula (V) or (VII) in which R^{10} represents a hydrogen atom or a hydroxy or methyl group;

(xiii) Z represents a group of formula (VII) in which R^{12} represents a hydrogen atom or a methyl group; or

(xiv) Z represents a group of formula

$-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{13}$ in which R^{13} represents an alkoxy or alkylamino group containing from 1 to 4 carbon atoms.

5. A compound according to any one of the preceding claims which is hereinbefore identified as any one of compounds A to CO.

6. A process for the preparation of a compound according to any one of the preceding claims which comprises:

a) where k is 0, reacting a compound of the general formula (VIII)

$$A-S-H \qquad (VIII)$$

wherein A is as defined in claim 1, or a salt thereof, of the general formula (IX)

$$A-S^- \ M^+ \qquad (IX)$$

wherein A is as hereinbefore defined in claim 1 and M represents an alkali metal, with a compound of the general formula (X)

$$X^1-Q-Z \qquad (X)$$

or a salt thereof, wherein X^1 is a group displaceable by a thiolate salt, and Q and Z are as defined in claim 1;

b) where k is 0 and Z represents a group of the formula $-NH-C(SR^3)=N-CN$, as defined in claim 1, reacting a compound of the general formula (XI)

$$(R^3S)-C(SR^3)=N-CN \qquad (XI)$$

wherein R^3 is as defined in claim 1 with a compound of the general formula (XII)

$$A\text{-}S\text{-}Q\text{-}NH_2 \qquad (XII)$$

wherein A and Q are as defined in claim 1;

(c) where k is 0 and Z represents a group of the formula $-NHR^2$ wherein R^2 represents an acyl group, acylating a compound of formula (XII) as hereinbefore defined;

(d) where k is 0 and Z represents a group of the formula $-CH(OH)CH_2(CR^9R^{10})_rCH_2COR^{14}$ wherein R^9, R^{10} and r are as defined in claim 1 and R^{14} represents a straight- or branched-chain alkoxy group containing from 1 to 4 carbon atoms, reacting a compound of formula (IX) as hereinbefore defined, with a compound of the general formula (XIII)

$$R^{15}CH_2(CR^9R^{10})_rCH_2COR^{14} \qquad (XIII)$$

wherein R^9, R^{10}, r are as defined in claim 1, R^{14} is as hereinbefore defined and R^{15} represents a 1,2-epoxyethyl group; or

(e) converting a compound of general formula (I) to a further compound of general formula (I);

and, if desired, converting the product thus obtained to a pharmaceutically acceptable salt.

7. A pharmaceutical composition which comprises an imidazole derivative of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or coating.

8. A pharmaceutical composition useful in the treatment of a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-

A:cholesterol-O-acyl transferase or an inhibitor of the binding of thromboxane TXA_2 to its receptors which comprises an amount effective to ameliorate said condition of an imidazole derivative of general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

9. A method of treatment of a human or animal host suffering from, or subject to, a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase or of an inhibitor of the binding of thromboxane TxA_2 to its receptors which comprises the administration to said host of an imidazole derivative of general formula (I) as defined in claim 1 or a pharmaceutically acceptable acid addition salt.

INTERNATIONAL SEARCH REPORT

of D3

International Application No PCT/GB 91/00408

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 233/84, A 61 K 31/415, C 07 D 405/12, C 07 D 403/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 233/00, A 61 K 31/00, C 07 D 405/00, C 07 D 403/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0019688 (CIBA-GEIGY AG) 10 December 1980 see the whole document	1-7
A	FR, A, 2380264 (E.I. DU PONT DE NEMOURS AND COMPANY) 8 September 1978	
A	EP, A, 0000353 (CIBA-GEIGY AG) 24 January 1979	
A	EP, A, 0323148 (SMITHKLINE BECKMAN CORP.) 5 July 1989	
A	EP, A, 0005545 (SCHERING AKTIENGESELLSCHAFT) 28 November 1979	

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13th June 1991	07. 08. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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P,X	EP, A, 0372445 (E.I. DU PONT DE NEMOURS AND COMPANY) 13 June 1990 see page 5; figure form. (I); page 6, lines 2,11,17 - page 20; page 9; figures form. 6,7; page 10, lines 39-42 --	1-9
P,X	Patent Abstracts of Japan, volume 14, no. 377 (C-748)(4320), 15 August 1990, & JP, A, 2138263 (NIPPON CHEMIPHAR CO. LTD), 28 May 1990 see the whole document --	1-2,6-7
P,A	EP, A, 0411908 (MERCK & CO. INC.) 6 February 1991 --	
P,A	EP, A, 0391796 (RHONE-POULENC SANTE) 10 October 1990	

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/00400

SA 45505

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 01/07/91
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB91/00408

SA 45505

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